INTRODUCTION TO CLINICAL ENDOCRINOLOGY

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PREFACE

I HAVE attempted to present clinical endocrinology in terms of applied physiology For this reason the book contains more information on hormones than on endocrine glands and only scant mention of pathological processes not accompanied by disorders of function. In aiming at coherence and simplicity I have sacrificed full discussion of alternative views and omitted references to the literature thereby failing to pay tribute to those whose discoveries have illuminated endocrinology All these points are well covered in full textbooks of endocrinology to which this work is an introduction. However I have included a short reading list for those who wish to make a more comprehensive study of the subject.

The absence of illustrations is due partly to economic considerations and partly to my deliberate choice Photographs show with dramatic clarity the grotesque end point of disease yet seldom portray fully the early clinical signs This may give a visual bias against early diagnosis Personally I believe that the student will learn more from the careful examination of one patient than from an album of photographs

It is a pleasure to record my gratitude to Dr Russell Fraser and Dr John Ellis for accepting the onerous task of correcting the manuscript and for their most helpful criticism I am indebted to Mrs E Scott for the low calcium diet printed in the appendix and to Mrs M Stone for her help with the typescript I would also liked to thank my publishers for their constant help which has made my path smooth Finally I am deeply grateful to my wife for her untiring work in all stages of the preparation of this book

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CHAPTER I

GENERAL PRINCIPLES

CLINICAL endocrinology is not concerned solely with fat boys and bearded women nor is it an esoteric cult based on the application of bizarre eponyms to apparently unrelated physical signs As the endocrine system plays a large part both in health and in many types of disease the proper approach to the subject lies through a knowledge of physiology and general medicine which must be broadened to include certain aspects of gynaecology neurology and paediatrics

Until the beginning of the twentieth century the central nervous system was considered to be the sole co-ordinating mechanism of the body the concept of chemical integration of the organism grew with the development of chemical physiology The idea of a chemical messenger secreted by a cell to influence the working of some distant part of the body was crystallized by Bayliss and Starling (1902) when they introduced the word hormone (Greek ὁρμάω — I stimulate) The synthesis and secretion of hormones is the primary function of the endocrine glands

The endocrine glands are so called because their secretions are discharged directly into the blood stream All these glands secrete their hormones into the systemic circulation except for the pancreas whose islets of Langerhans secrete into the portal system A gland may be composed of cellular elements like the thyroid or of neural tissue like the adrenal medulla Within the gland the hormones are synthesized stored and finally secreted Some storage of hormone occurs in all glands but the thyroid is the only one with special storage space in the centre of each secretory unit It is important to remember this property of storage because it represents the difference between the rate of hormonal synthesis and secretion Hence a high concentration of hormone in the gland does not indicate activity so much as inhibition of secretion with continued synthesis Conversely the immediate response to stimulation is a discharge of stored hormone prior to an increase in the rate of synthesis with the result that hormone concentration in the gland drops sharply

Hormones are physiological substances some being proteins or polypeptides others steroid in nature They provide a humoral mechanism for the regulation of biological processes playing an important role in growth maturation reproduction and the maintenance of a constant

internal environment In their mode of action they resemble chemical catalysts exerting their influence not by the initiation of physiological mechanisms but by regulating the rate at which the mechanism operates

The exact nature of hormonal action is dependent on the characteristics of the hormone and the organ or organs on which it acts Any tissue which is the site of action for a hormone is termed an end-organ Some hormones act on one end-organ only others have a general effect as well as specific action on certain organs In the first category are the trophic hormones of the anterior pituitary each of which stimulates its specific endocrine gland and has no other action They exert an indirect action on the body as a whole through the gland they stimulate The second category is illustrated best by the sex hormones For instance testosterone produces marked growth of the seminal vesicle This growth entails protein anabolism At the same time the hormone stimulates the anabolism of protein throughout the body Similarly oestrogens cause a marked retention of water in the uterus and some retention of water in other tissues Moreover the general effects of these two hormones are roughly similar both causing retention of water and calcium yet their effects on the sexual end-organs are directly opposed This illustrates the concept that few hormones are completely specific by virtue of their intrinsic properties but that specificity is conferred by the responsiveness of end-organs This also applies to the hormones which have a wide effect on metabolism such as thyroxine growth hormone and hydrocortisone Thyroxine influences the metabolic rate water balance and vascular system of the body its variety of actions depending on the reactivity of specific physiological mechanisms rather than specific organs

The interaction of hormone and end-organs is of fundamental importance in clinical study as disorders of function may arise from changes in the level of circulating hormone or the sensitivity of the end-organ to hormone action The effect of hormone deficiency on an organ is imitated by a failure of that organ to respond to normal hormonal stimulation For instance eunuchs have no beard because the testes are not functioning But the healthy Red Indian male never grows a beard by virtue of his genetic constitution yet his virility is unquestionable Another example is provided by the difference in the clinical picture of thyrotoxicosis according to the age of the patient In the elderly the disease commonly presents with cardiac manifestations which do not occur in the young The hormonal stimulus is the same in all age groups but the elderly heart reacts rapidly to a small increase in circulating hormone Thus genetic biochemical and age factors influence the interaction of one hormone and its end-organ

In clinical medicine one observes the final result of this interaction It is obvious that physical signs are not a direct indication of the rate of hormone secretion.

Now the various physiological factors governing hormone action have been described the interdependence of the endocrine glands must be considered The amount of hormone produced by any one gland is subject to controlling influences which finally integrate the whole system These influences are of three main kinds Firstly the regulation of hormone secretion by the concentration of certain chemicals in the blood stream Secondly the control of activity by the anterior pituitary Thirdly the controlling influence of the hypothalamus correlating the endocrine and nervous systems

The simplest type of regulating mechanism analogous to the thermostatic control of a water heater is shown by the parathyroid glands which appear to have no other governing process than the concentration of calcium in the blood stream A more complex mechanism governs the posterior pituitary in which hormone secretion is directly related to the osmotic pressure of the blood but is also subject to nervous control through the hypothalamus which may over ride the primary homeostatic mechanism

The anterior pituitary exerts an overall effect by the secretion of a number of trophic hormones which govern the action of the glands they stimulate Thyrotrophic hormone (T S H) regulates the activity of the thyroid and adrenocorticotrophin (A C T H) the activity of the adrenal cortex There is a reciprocal relationship between the amount of trophic hormone released by the pituitary and the level of circulating hormone from the stimulated gland In essence this feed-back mechanism is similar to the homeostatic control of the glands already described The action of a hormone in suppressing the pituitary appears to be limited to inhibition of its specific trophic hormone hence administration of thyroxine will only suppress the output of thyrotrophic hormone There are important clinical implications in this pituitary-target gland relationship On the one hand the administration in non-endocrine disease of large doses of cortisone suppresses the secretion of adrenocorticotrophic hormone with consequent adrenal inactivity Hence abrupt cessation of treatment will leave the patient in a state of adrenal hypofunction with all its attendant dangers On the other hand the mechanisms can be used deliberately as in the administration of oestrogen for the treatment of carcinoma of the prostate The oestrogen inhibits the output of gonadotrophin with resultant testicular atrophy It acts via the pituitary as a medical castration. There is also a diagnostic use particu-

larly in hypogonadism If the disturbance is due to destruction of the gonad the low level of circulating sex hormone will give rise to an excessive secretion of gonadotrophins However gonadal atrophy from failure of pituitary stimulus will be associated with a very low level of gonadotrophin secretion Assay of the excreted gonadotrophin enables the clinician to decide which type of hypogonadism is present

The last link in endocrine *integration lies between the hypothalamus* and the pituitary As this provides a connection between the higher cerebral centres the autonomic system and the endocrine system the link is of the greatest importance Unfortunately its details remain obscure and even its nature is in doubt It is most probable that the hypothalamus has a regulating effect on the anterior lobe of the pituitary by some humoral mechanism there is certainly no evidence for a neural connection The regulating effect can be illustrated by the effect of the hypothalamus on sexual maturation Experiments have shown that the pituitary synthesizes gonadotrophins some time before the onset of puberty The release of these hormones which set off puberal sex growth is due to a stimulus from the hypothalamus It is not surprising that lesions of the hypothalamic area in humans are often associated with precocious or delayed puberty There is also experimental evidence for hypothalamic regulation of the secretion of thyrotrophic and adrenocorticotrophic hormones In the case of thyrotrophin the hypothalmus appears to alter the quantitative aspects of the pituitary-thyroid feed-back mechanism The level of circulating thyroid hormone required to suppress the pituitary activity is changed If the pituitary-thyroid regulation is akin to the thermostat then the hypothalamus acts like the control which adjusts the temperature at which the thermostat will operate

Much has been said on the production and action of hormones without a mention of their eventual fate This is not because the subject is unimportant but rather because so little precise information is available The blood level of a hormone is the balance between secretion and destruction so that variation in the speed of destruction may influence profoundly the amount of available hormone However even the sites of destruction are not fully known Whether or not a hormone is destroyed by the tissue on which it acts is still undecided. But it is clear that the liver inactivates many of the steroid hormones and diseases of the liver may be associated with endocrine dysfunction due to failue of hormone inactivation

It is now possible to summarize these generalizations in terms of clinical endocrine disorders All such conditions arise from some disturbance of the normal endocrine equilibrium Primary endocrine disease can be

conceived as a failure at any point in the basic pattern of hormone production destruction and end-organ response Hypothyroidism is due to failure of secretion by the thyroid either because it has been destroyed (primary myxoedema) or because its pituitary control has failed (pituitary hypothyroidism) or from selective failure of hormone synthesis (certain types of goitrous cretin) If however production of a hormone is normal failure of destruction results in an excess of circulating hormone as in cirrhosis of the liver which may be associated with gynaecomastia from excess oestrogen Lastly the varying response of the end-organ to a given amount of hormone may determine the clinical picture A rare but interesting example of this is pseudo-hypoparathyroidism, in which the body is completely unresponsive to its own or injected parathyroid hormone The resultant tetany with low serum calcium is exactly similar to that occurring after removal of the parathyroids

The situation is more complicated when a single pathological process causes more than one endocrine disturbance as is seen commonly with lesions of the anterior pituitary An acidophil adenoma producing an excess growth hormone will press on the rest of the gland so that secretion of other hormones is reduced The interplay of various hormones may also lead to more than one disorder thus evidence of adrenal hypofunction is common in myxoedema because the adrenal is affected by the lack of thyroid hormone Correct diagnosis depends on a careful appraisal of such interactions with the avoidance of such terms as pluriglandular disorder which is merely a substitute for thought

It is too easy to assume that primary endocrine disease is the cause of certain syndromes Dwarfism will result from destruction of the pituitary in a child but it does not follow that all dwarfs lack a pituitary But this does not minimise the role of the endocrine system in various types of disease The malnutrition of coeliac disease is associated with infantilism because pituitary function is depressed Similarly lesions of bone arising in long standing renal failure are linked with parathyroid hyperplasia It is important to keep endocrinology in the field of general medicine and to realize how many diseases have an endocrine aspect and how diseases of the glands masquerade as more general conditions

CHAPTER II

THE HYPOTHALAMUS AND POSTERIOR PITUITARY

Anatomy and Physiology

There is every justification for a composite description of the hypothalamus and posterior pituitary for although the two lobes of the pituitary are contiguous they differ in origin structure and function while the posterior lobe is linked to the hypothalamus by form and function

In embryo the posterior pituitary arises as a diverticulum passing downwards from the third ventricle When fully formed the lobe consists of neural tissue which continues up the pituitary stalk to the hypothalamus forming one functional unit the supra-optico-hypophyseal tract The hypothalamus itself forms the basal portion of the diencephalon lying in relation to the floor and lower part of the walls of the third ventricle Anatomically speaking it comprises the optic chiasma pituitary tuber cinereum and corpora mamillaria In physiological terms the latter two structures are usually called the hypothalamus

The hypothalamus provides a connecting link between the cerebral cortex whose stimuli it receives and various homeostatic mechanisms on which it exerts a regulatory effect Its effects are mediated by neural pathways particularly through the autonomic system by the neuro-secretory mechanisms of the posterior pituitary and by an influence on the anterior pituitary There are no neural connections between the hypothalamus and the anterior pituitary but there is a portal system of blood vessels which links the two structures It is probable that this allows for some humoral mechanism by which the anterior pituitary is influenced by the hypothalamus

Certain metabolic functions under the control of the hypothalamus are of considerable importance in endocrinology Correlation of experimental work and human autopsy material has given some indication as to the anatomical localization of the controlling centres but much of the physiology remains obscure However the endocrine and metabolic aspects of hypothalamic function may be classified as follows

(1) Regulation of energy balance

control of { sleep / body temperature / appetite

(2) Regulation of sexual function.
(3) Influence on carbohydrate metabolism
(4) Control of water balance

The normal rhythm of sleep is controlled by centres in the lateral hypothalamus Lesions of this area result in narcolepsy and other disturbances of sleep

The maintenance of a normal body temperature despite varying environmental temperatures depends on centres in the tuber cinereum Both heat production and heat loss are under their influence Breakdown of this mechanism is followed by great variations from the normal body temperature Acute lesions are often associated with hyperthermia the body temperature rising to 106° or more

The paraventricular nuclei exert a marked effect on the appetite for food Destruction of these nuclei in experimental animals is followed immediately by a dramatic increase in appetite The food intake in one day may be equal to the body weight It follows that marked obesity is a common clinical feature of hypothalamic disease Little is known of the normal control of appetite but there are good grounds for assuming that the paraventricular nuclei play an important role

The areas concerned with sex function are ill defined and there does not seem to be any exact localization The mamillary bodies appear to exert a controlling influence on the secretion of pituitary gonadotrophins The anterior pituitary manufactures gonadotrophins prior to puberty but the release of these hormones is dependent upon a stimulus from the hypothalamus which initiates puberty Likewise the maintenance of a normal menstrual cycle is dependent on a complicated interplay of gonadotrophins whose release is controlled by the hypothalamus Consequently lesions in the area of the corpora mamillaria are associated with abnormalities in the age at which sexual development occurs on the one hand precocious puberty and on the other delayed development or sexual infantilism In adults gonadal atrophy can occur but the most obvious sign is amenorrhoea

Alteration in the body s sensitivity to insulin due to the effect of the autonomic nervous system may give rise to hypo- or hyper-glycaemia Clinically this effect is usually transitory in association with acute lesions In very rare instances an insulin resistant hyperglycaemia becomes permanent

The supra-optico-hypophyseal tract secretes two hormones both recently identified and synthesized The two hormones are very similar

in structure both being polypeptides The first oxytocin, causes contraction of the uterus although its role in human physiology is uncertain The second vasopressin causes vasoconstriction and inhibits water diuresis It is unfortunate that the name vasopressin is used because its normal physiological role is in the control of water balance rather than blood vessel tone Antidiuretic hormone (A D H) is a better name as it represents the physiological action of the hormone Secretion of A D H is determined by impulses from the cerebral cortex and by osmoreceptors in the hypothalamus Hence variations in emotional state are associated with changes in the output of A D H Strong emotions such as fear result in marked diminution of urine output However body water balance is controlled largely by the osmoreceptors Intravenous infusion of hypertonic saline in the normal subject results in a decrease in urinary output Loss of body water causes a rise in the osmotic pressure of the blood which leads to an increased output of A D H so that water loss via *the kidney is diminished Conversely a decrease in osmotic pressure* inhibits A D H secretion so that excess water is passed out through the kidneys Diuresis after the ingestion of a large quantity of water is dependent on this mechanism It has also been found that injection or inhalation of nicotine stimulates the secretion of A D H providing a valuable test of hypothalamic function

A D H regulates water balance solely by acting on the distal tubules of the kidney It is in this part of the kidney that water resorption occurs and the quantity resorbed is governed by the amount of circulating A D H There is no evidence that A D H has any other renal effect in the human *its action is related entirely to the conservation of water* and has no direct effect on the excretion of electrolytes Of course an increase in urine volume by virtue of diminished water resorption will be accompanied by a fall in the urinary concentration of chloride and specific gravity but chloride excretion itself is not dependent on A D H

There is one important factor that influences water resorption by the kidney in relation to A D H For many years it has been known that injury to the posterior pituitary with failure of A D H secretion is followed by polyuria only when the anterior pituitary is intact Recent work has shown that it is the maintenance of normal adrenal function that allows polyuria when A D H is absent Thus experimental work is con*firmed by clinical experience for a slow growing tumour which initially* destroys the supra-optico-hypophyseal tract will cause polyuria but at a later stage when the anterior pituitary is destroyed the polyuria diminishes Moreover polyuria will return if A C T H or cortisone is

administered to the patient If the hypothalamic area is intact but the adrenal ceases to function, as in Addison s disease diuresis does not follow an ingested water load. The capacity to secrete a water load is restored by the administration of cortisone This complicated and ill-understood piece of physiology does have clinical importance and will be referred to again in relation to diseases of the anterior pituitary and adrenal

Diabetes Insipidus

The disorder of function is a failure of renal water resorption due to an ineffective circulating level of A D H Lesions of the supra-optico-hypophyseal tract cause the disease by diminishing or destroying the secretory capacity of this tissue In rare instances the syndrome is produced by insensitivity of the renal tubules to the action of A D H in the absence of other evidence of renal failure

Aetiology

The disease is more common in males and is predominantly an affliction of childhood or early adult life Clearly the lesion may often be such as to give rise to a general clinical picture of which diabetes insipidus is only a small part, and therefore the diagnosis of diabetes insipidus must always be followed by a systematic appraisal of the patient for other disorders of function. The very varied aetiology of the lesion is as follows

(1) *Idiopathic*

A localized presumably degenerative lesion of the supra-optico-hypophyseal tract occurring in children or young adults with no other disturbance of function This is a rare form of the disease and the diagnosis must be regarded with suspicion. All too often the development of other clinical disturbances some time after the onset of diabetes insipidus makes it obvious that the aetiology is not idiopathic

Several family histories have been recorded in which many members of succeeding generations are afflicted. In some families the disease is resistant to injected A D H and may be presumed to be due to renal tubule insensitivity and not to hypothalamic dysfunction

(2) *Infection*

Many forms of chronic meningitis or arachnoiditis may cause the disease with associated neurological disturbances

(3) *Xanthomatosis*

In children the Hand-Schuller-Christian syndrome is associated with diabetes insipidus in over 50 per cent of cases In adults generalized

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of posterior pituitary extracts A rare syndrome in early childhood is nephrogenic diabetes insipidus which is a specific failure of tubular response to A D H in the presence of otherwise normal renal function These water-babies show no evidence of a hypothalamic lesion and do not respond to injected posterior pituitary extract.

Psychogenic polydipsia provides the major difficulty in diagnosis As an hysterical phenomenon, intense thirst will be followed by polyuria if the water intake is excessive Thirst is the primary symptom as compared to the primary polyuria of diabetes insipidus The clinical differentiation of the two conditions may be very difficult if there is no evidence of organic disease and no other stigma of hysteria Three forms of test are of diagnostic use

The most reliable procedure employs a water load with stimulation of the supra-optico-hypophyseal tract by nicotine (inhaled or ingested) Provided fainting which alters renal blood flow is avoided the test gives a valid index of hormone secretion which can be compared to the effect of intravenous A D H on water diuresis By this means diabetes insipidus can not only be diagnosed by the failure of nicotine to inhibit diuresis but the sensitivity of the kidney to A D H is determined as well However it must be noted that the test requires careful attention to technical detail before good results are obtained

Another test is based on the stimulation of the osmoreceptors by hypertonic solutions Water diuresis is promoted by the ingestion of water and then hypertonic saline is infused intravenously The diuresis will cease in the normal and continue in diabetes insipidus The objection to this routine lies in the salt load which the kidney has to handle The result may not indicate excretion of water as an osmotic diuresis may arise

The simplest procedure is the withholding of water for as long as the patient can tolerate it In diabetes insipidus polyuria continues with no rise in the specific gravity of the urine and loss of body weight the volume of urine passed by the hysteric will diminish markedly with a considerable rise in specific gravity and there is no loss of weight Unfortunately the test often fails because the hysteric will not suffer water deprivation even when sedated. Moreover the kidney adapted to producing large quantities of urine will not suddenly conserve water when the patient s intake is stopped So the test is useful in excluding diabetes insipidus when the urine output drops and the specific gravity increases but if this does not occur then the patient still may or may not have diabetes insipidus

xanthomatosis often with pulmonary involvement may give rise to the disease

(4) *Trauma*

Fractures of the skull base or operations in the region of the hypothalamus commonly give rise to a transient form of the disease In some cases the condition becomes permanent

(5) *Tumours*

Many types of tumour both primary and secondary give rise to the disease and commonly affect other aspects of hypothalamic function The growths may be situated around the third ventricle or in the posterior fossa

CLINICAL COURSE

The prime symptoms are gross polyuria and thirst The urine is free of abnormal constituents but has a constantly low specific gravity (about 1002) The polyuria is constant the volume passed at night being equal to that of the day As the capacity of the bladder increases very large quantities are voided each time it is emptied The thirst is persistent and agonizing patients will drink from puddles or even their own urine in an effort to assuage it As the disease progresses dehydration gradually appears the weight falls the skin becomes dry and inelastic and the lips parched and cracked Intense thirst kills an appetite for food and destroys sleep Loss of water from the body causes constipation and it also causes some salt loss with resultant muscle weakness and cramps It is a miserable condition in which the patient s life is confined between the water jug and the lavatory

The natural history of the disease is dependent more on the general effects of the causative lesion than on the disturbance of water balance Normal hydration can be maintained indefinitely with pitressin therapy Occasionally idiopathic diabetes insipidus ends with spontaneous cure If a tumour gives rise to the condition it may destroy the anterior pituitary with amelioration of the polyuria

DIAGNOSIS

Thirst and polyuria are prime symptoms of diabetes mellitus which is distinguished immediately by the presence of glycosuria The same symptoms may be marked in certain cases of renal failure but here the presence of albuminuria and uraemia makes the diagnosis clear Polyuria in such cases is due to failure of the renal tubules to respond to A D H This can be demonstrated by the continued diuresis despite the injection

patient s lesion developed his appetite became so excessive that the cafe proprietor paid him to dine elsewhere It is not surprising that the degree of obesity is usually marked with body weights over 30 stones

The aetiology of this syndrome is similar to that of diabetes insipidus which may be an associated disturbance A transient form of the condition also occurs most commonly due to mental disturbance but occasionally from organic causes In this there are repeated attacks each lasting one to three days of somnolence disturbed water balance and polyphagia

The treatment must be directed to the causative lesion. The disturbance of function is amenable to amphetamine sulphate which will control the narcolepsy and the polyphagia Large doses are required but evening administration is to be avoided in case it interferes with the night s sleep Total daily dosage may reach 400 mg but the necessity for such a large dose should be demonstrated by failure of response to more routine dosage (30-60 mg daily)

Frohlich s Syndrome

Frohlich s one case was a male apparently healthy until the age of twelve years when he started to experience severe headaches vomiting and loss of visual acuity With the onset of these symptoms the boy became obese the adipose tissue being most marked around the pelvis and genitalia giving rather feminine contours The limbs were also obese the pudgy fingers tapering towards the tip He failed to develop sexually at the age for normal puberty but his height was apparently normal for his age By the age of twenty years sexual infantilism was still apparent but the obesity had not progressed to any degree Operation revealed a tumour involving the area of the pituitary and hypothalamus

Thus the essentials of the syndrome are obesity sexual infantilism and a space-filling lesion in the pituitary-hypothalamic region At first it was considered to be a primary disorder of pituitary function but later experimental work made it quite clear the obesity does not arise from pituitary destruction but only from hypothalamic damage Moreover delay of sexual development also follows hypothalamic lesions Human autopsy material confirms this work destruction of the anterior pituitary without damage to the hypothalamus has not been found in association with Frohlich s syndrome The type of tumour which gives rise to the syndrome is the craniopharyngioma or a chromophobe adenoma of pituitary with suprasellar extension. Occasionally suprasellar cysts of various types are the causative lesion

It is obvious that true Frohlich s syndrome is a rare entity and one that

In the near future it is likely that assay methods for A D H will prove to be the most specific diagnostic test as absence of antidiuretic factors from the patient s serum in a state of thirst would be indicative of diabetes insipidus

TREATMENT

Extracts of posterior pituitary containing A D H are available in three forms The aqueous extract (pitressin) for injection lasts about eight hours so that an evening dose ensures a night s sleep Reasonable control of the disease can be achieved by twice daily injections of 5-15 units Overdosage results in peripheral vasoconstriction a rise in blood pressure and intestinal spasm Continued excessive intake of water after a therapeutic dose of pitressin may result in temporary water poisoning It is wise therefore to give an initial dose of 5 units to be increased by 5 units until the polyuria is controlled Therapy has become far more convenient since the introduction of pitressin tannate (in oil) a slowly absorbed preparation with an action spread over at least 24 hours Sometimes injections on alternate days will prove sufficient Failure to achieve good *results with pitressin tannate is often due to insufficient shaking of the* ampoule so that little of the active content is drawn down into the syringe A dry powdered extract of posterior pituitary is available in the form of snuff This is particularly suitable for children who are obviously much happier to sniff a powder up their nose than to have repeated injections The amount of snuff required is a matter of practical trial but several pinches a day are needed Unfortunately the snuff is ineffective in the presence of nasal catarrh and sometimes the powder irritates the nasal mucosa with resultant mucous discharge

The patient must be made to understand that an attempt to cure the *condition by limiting the fluid intake is dangerous and that treatment* must control the polyuria first

Sexual Precocity

The relationship of the hypothalamus to an early onset of puberty will be discussed in a later section (page 136)

Obesity and Narcolepsy

Dickens fat boy is a good example of the syndrome in which polyphagia is associated with disturbed sleep rhythm and narcoleptic attacks One of the *first reported cases* concerned a Frenchman who used to eat at a cafe which allowed its customers free bread with their meals As the

gests that if the bulk of the day s intake of food is consumed in one meal there is a greater likelihood of a positive energy balance than if it is consumed in several small meals It is a common observation that obese people favour one good meal a day Lastly water retention may account for some of the weight gain by the obese patient Of course water is also retained in adipose tissue so that when a negative energy balance is created by dietary means the weight does not fall at a regular rate in step with the daily caloric deficit but in an irregular fashion as fat plus water is lost Apparent failure to lose weight initially on a correctly administered reducing diet is due to this failure of water excretion.

The endocrine system plays an indirect role in obesity It may diminish the body s caloric requirements by a drop in metabolic rate alter the ratio of fat to protein in the body or determine the sites at which adipose tissue is laid down But these effects will not lead to obesity unless the food intake remains in excess of caloric requirements The metabolic rate falls in hypothyroidism but the degree of adiposity in such patients varies widely according to whether the appetite is impaired or not Similarly in adrenal failure the metabolic rate is lowered but anorexia is a very constant symptom so that weight loss is a feature of the disease In adrenal hyperactivity of the Cushing type obesity is common as the excess of hydrocortisone increases the percentage of body fat at the expense of protein and also encourages the appetite If anorexia occurs then the patient will lose weight in a perfectly normal fashion The adrenal hormones also determine the characteristic face and trunk distribution of adipose tissue although the degree of adiposity is dependent on food intake A further example of this is hypogonadism Male eunuchs vary from lean to obese but if they are obese the fat is laid down around the lower abdomen and genitalia Obesity may follow an artificial menopause but it is not directly due to cessation of ovarian function in that not all the patients gain weight and adequate hormonal therapy does not alter the obesity when present

The bodily constitution plays a large part in determining the capacity to become obese Hereditary characters are involved here and it is very common to find generations of a family who are all lean or of another family who are plump Sometimes this is not due to constitutional development but to acquired familial eating habits Many families are used to a high fat or carbohydrate diet and so do not consider they are eating too much To some mothers a fat child is evidence of good maternal care or material success in the world Other people eat when they are worried and consume snacks as a chain smoker consumes cigarettes

should not be diagnosed before the age of puberty Unfortunately the diagnosis has been used for all types of fat boys some with delayed puberty others with normal genitalia so buried in pubic fat that they appear small on inspection This problem of childhood obesity is discussed in the next section

Laurence-Moon-Biedl Syndrome

The diagnosis of this congenital defect of germ plasm is made on finding the following defects

(1) Generalized obesity
(2) Sexual infantilism
(3) Mental deficiency
(4) Atypical retinitis pigmentosa
(5) Polydactyly
(6) Other congenital defects e g atresia ani renal abnormalities etc

The syndrome is twice as common in males as in females and the familial incidence is most marked Not all the cases exhibit every feature of the full syndrome It is an unrewarding disorder in that it is recognizable immediately and untreatable It should be considered as a collection of congenital defects and not as a primary endocrinopathy In the few autopsies reported no significant histological lesion of the hypothalamus or pituitary has been found

The Problem of Obesity

The indiscriminate diagnosis of endocrine obesity has driven an exasperated doctor to exclaim that the only glands involved in obesity are the salivary glands Despite the poetic licence of this view it is true that obesity which is the accumulation of excessive fat is primarily a disturbance of energy balance Even the most ingenious patient cannot defy the laws of thermodynamics Weight gain by deposition of fat is achieved only by a positive energy balance the caloric intake in food exceeding the output in body work There is no evidence that the obese patient differs from the thin person in the efficiency of food absorption specific dynamic action of certain foods or in caloric output for a given amount of work It follows that the obese person must differ from his slimmer colleague either by greater food intake or less body work Differences in the quality of diets which are iso-caloric play some part as a high proportion of protein exerts a specific dynamic action which is not possessed by a high carbohydrate diet Experimental evidence sug-

adolescence. The response to a balanced diet is illuminating because both acne and pink striae will disappear if the condition is merely a minor disturbance of puberty

In boys a different body configuration is common, the general obesity being accentuated by adiposity around the hips lower abdomen and over the pectoral muscles A late onset to puberty with the genitalia submerged in pubic fat lends a further suggestion of femininity to the body contours When puberty occurs face hair is usually scanty and the pubic hair does not grow up towards the umbilicus The eventual growth is perfectly normal and the boy becomes a well built normal male The condition is described accurately by the term adipose gynandrism but although one may recognize this as a variety of normal development it is doubtful whether it can be considered as a definite syndrome Dietary treatment for this obesity is necessary but endocrine therapy is unwarranted unless sex development is unusually delayed, when treatment should be as for any case of delayed puberty (see pages 146 and 156)

In both sexes orthopaedic deformities are common because of the mechanical strain of obesity Genu valgum and pes planus are common an increased incidence of slipped epiphyses is also observed

Obesity in Pregnancy and Lactation

Brief mention must be made of obesity arising in pregnancy and continuing in the period of lactation. Weight gain occurs with each successive pregnancy and lactation may be profuse and prolonged The birth weight of the children is well above normal in many instances When these patients reach middle age they are prone to develop diabetes mellitus This association of obesity large babies and eventual diabetes is of uncertain aetiology but considerable interest

Indeed there are many similarities in the psychological stresses afflicting the chain smokers and the snack eaters Both would vehemently deny an excessive indulgence in their favourite pleasure Of course denial of excessive eating may be valid by the time the patient sees a doctor A positive energy balance is only present during the dynamic phase of obesity when fresh adipose tissue is being laid down In the static phase which lasts for many years there is no further increase in weight and the food requirement to maintain a caloric equilibrium is within normal limits To discover these facts the services of a skilled dietician are most valuable A proper dietary history will reveal many well concealed calories Indeed one can conclude that overeating is 90 per cent of the cause in 90 per cent of obese people

Particular Types of Obesity

Obesity in Children

The overnourished child is not only obese but usually tall and broad for his or her age contrasting with the decrease in growth rate seen in Cushing s syndrome or in organic disorders of the hypothalamus Most mothers consider that something must be wrong with their children s glands if they become obese and few admit to overfeeding However it is significant that many obese children are only children with the dietary spoiling that mothers indulge in under the mistaken impression that the child must be fed Over-dependence on mother and little physical activity make eating a major hobby for these patients Undoubtedly constitutional factors are also important but careful dietary histories will reveal an unbalanced and excessive diet An appreciation of the relationships of mother to child is very necessary if their co-operation is to be gained in carrying out the necessary dietary alterations

Obesity in Adolescence

Obese girls of broad tall build usually go into puberty rather earlier than the average normal age As secondary sex characters develop a greasy skin and acne may be troublesome Small pink striae may appear on the abdomen upper thighs and round the axilae These signs are perhaps suggestive of Cushing s syndrome However the normal or increased stature general obesity with normal muscle bulk and the small size of the striae which are pink rather than lilac distinguish the benign disturbance of puberty from the serious and very rare Cushing s syndrome In some instances distinction is more difficult as there is no doubt that adrenal function can vary through a wide range of normality during

HORMONES OF ADENOHYPOPHYSIS

Class	*Name*	*Action*
(1) Direct Action	Growth Hormone (G H) (Somatotrophin)	Stimulates growth of body protoplasm (including skeleton) Diabetogenic under certain circumstances
(2) Action on Endocrine glands only (trophic hormones)	(a) Adrenocorticotrophin (A C T H)	Stimulates growth of adrenal cortex and production of its hormones
	(b) Thyrotrophin (T S H.)	Stimulates growth of thyroid cells and release and production of hormone
	(c) Gonadotrophins (1) Follicle stimulating hormone (F S H) ( ) Luteinizing Hormone (L H)	Stimulates growth of gonads product on of hormones and regulation of reproduction
	(3) Luteotrophin (Prolactin)	Affects milk production and corpus luteum

ACTION OF GROWTH HORMONE

Hypophysectomy in the young animal is followed by cessation of growth The administration of growth hormone will restore the rate of growth to normal without correction of the other endocrine deficiencies The degree of growth is proportional to the dose of hormone prolonged administration of large doses produces a giant animal of normal proportions Metabolic studies show that growth hormone promotes protein anabolism the nitrogen balance being strongly positive together with a lowering of the plasma amino acid concentration and a rise in serum inorganic phosphorus The diversion of dietary protein from energy-producing catabolism to the anabolic activity of body building alters the composition of the body so that the amount of protein increases at the expense of fat The skeleton is stimulated to growth in the same manner intense activity appearing at the growing end of the bone But growth hormone has little effect on the maturation of the epiphyses or their closure Thus the bones will continue to grow in length provided the epiphyses remain unclosed but longitudinal growth will not result from growth hormone if the epiphyses are already closed Consequently excess of growth hormone will produce gigantism in the child but acromegaly in the adult The organs of the body share in the growth process excessive overgrowth of tongue and skin are immediately obvious to the clinician Endocrine organs increase somewhat in size in response to growth hormone but they show no histological evidence of maturation and no functional response In fact growth hormone pro-

CHAPTER III

THE ANTERIOR PITUITARY (ADENOHYPOPHYSIS)

Anatomy and Physiology

In the embryo the adenohypophysis arises from an upward evagination of *the stomodaeum When fully formed the gland lies in the sella turcica* a hollow on the upper surface of the sphenoid bone Posteriorly the gland is related directly to the vestigial pars intermedia and the posterior pituitary There is a double blood supply a systemic one derived from the internal carotids and a portal system lying around the pituitary stalk which connects the adenohypophysis to the hypothalamus It has been stated already that this may be the pathway for some humoral mechanism by which the hypothalamus exerts its regulatory function on the anterior pituitary

The gland is a cellular structure in which classical staining methods reveal three cell types chromophobe acidophil and basophil Chromophobe cells do not appear to have secretory activity but there is good clinico-pathological evidence to show that acidophil cells are associated with growth hormone and basophil cells with adrenocorticotrophin However modern histochemical methods indicate that the older staining methods are too crude to allow a close analysis of cytology and function but suggest that each hormone is produced by a specific cell For the moment is is more profitable to accept the traditional classification of cell types as a generalization than to speculate further on the details of the subject

The adenohypophysis liberates several hormones all of which are polypeptide or protein in nature These hormones have been extracted in physiological rather than chemical purity and a great deal remains to be done on their chemical identification Six hormones are now recognized as distinct entities produced by the adenohypophysis as shown in the table on page 19

The roles of the hypothalamus and the circulating level of hormone from the target gland *in the control of pituitary hormone secretion* have been discussed fully in Chapter I The action of the trophic hormones on their target glands will be described in the chapters devoted to these glands

tion of the adenoma may occur with destruction of the rest of the pituitary The resultant hypopituitarism is particularly severe in that the patient has such a large body and is so weak. Luckily this unfortunate termination is rare \ The main problem of gigantism lies in the fact that the affected child becomes a freak. It is most difficult for a child to be well adjusted and happy among his fellows when he is physically so different from them The problem is particularly acute for a girl

DIAGNOSIS

The diagnosis of pituitary gigantism is certain if the body is of normal proportions the growth rate excessive and the sella turcica expanded. The presence of acromegalic features is further proof The condition must be distinguished from constitutional tall stature which is of genetic origin has a high familial incidence and is not associated with anterior pituitary enlargement X-ray of the skull and an adequate family history will aid the distinction In children precocious sexual development is associated with a somatic growth spurt The child becomes above the normal height but the correct diagnosis is apparent from the development of secondary sex characters and the X-ray evidence of early epiphyseal closure In adults eunuchoidal gigantism is easily differentiated in that childhood growth is normal the patient continuing to grow when an adult with delayed epiphyseal closure Moreover the growth is disproportionate the limbs being excessively long compared to the trunk, and secondary sex development is absent or minimal

TREATMENT

A conservative policy is advisable A period of observation is necessary to determine the activity of the growth disorder Unless it is progressive and the patient likely to become definitely deformed, it is wise to observe rather than treat The treatment is deep X-ray therapy to the pituitary Its possible effects on the other actions of the pituitary are the main reason for advocating caution in initiating treatment. But the effect of radiation on excessive growth hormone production is very good No other form of therapy has been found effective Premature fusion of epiphyses by administration of sex hormones has been advocated — this is not advised as induced sexual precocity with acromegalic changes will result

Acromegaly

Acromegaly meaning large extremities is the disorder which results from an excess of growth hormone acting on the adult body Hence the

motes protein anabolism and consequent increase in size but it does not promote maturation or development

The diabetogenic effect of certain pituitary extracts appears to be due to growth hormone by reason of its antagonistic effect on the peripheral action of insulin It antagonizes the action of insulin on the hexokinase cycle However growth hormone is not diabetogenic in all species or under all circumstances In man excessive secretion of growth hormone is by no means invariably associated with diabetes It is presumed that endogenous insulin production is increased to counteract the effect of growth hormone so that diabetes will occur only if insulin production cannot rise to the required level

Pituitary Gigantism

Gigantism is defined as a body height which is above the range of normality for the patient s race Pituitary gigantism is due to an excessive secretion of growth hormone associated with an eosinophilic adenoma of the pituitary There is little relation between the degree of hormone excess and the size of the adenoma Consequently localizing signs of a space-filling lesion of the pituitary fossa are usually absent despite marked gigantism Pure gigantism can only occur during childhood If the condition is progressive throughout adolescence when the epiphyses are closing a mixed picture of gigantism and acromegaly will result

Both sexes are affected the age of onset being very variable An early onset at 4-5 years of age leads to extreme gigantism with recorded heights up to 9 feet The growth is excessive but normal in character The later the onset the less the degree of gigantism and the greater the incidence of acromegalic features Its progress is followed best by comparing the growth curve with the curves for normal children The height of the patient will be above the upper range of normality and the growth curve deviating upwards away from the normal A return towards *the normal growth curve indicates remission of the disorder* Epiphyseal development remains normal and there is no evidence of sexual precocity Occasionally the growth spurt is so intense that acromegalic features appear in the thickening of the skin and coarsening of the face even when the patient is well below the age of epiphyseal closure Muscle bulk is not always matched by strength and the excessive height is not necessarily well supported Therefore postural defects such as kyphosis and scoliosis are common.

Gigantism in its active phase is a benign disease Diabetes mellitus appears to be a very rare complication. At a later stage cystic degenera-

considerable strength it is a common finding that muscle power is not as great as the bulk would suggest

The viscera are enlarged but liver and spleen are not palpable There may be enlargement of the heart either with or without hypertension Occasionally enormous hypertrophy of the myocardium occurs with a normal blood pressure but with electrocardiographic changes suggesting ischaemia Hypertension is probably more common in acromegalics than in the population as a whole It may be severe in degree and associated with papilloedema Heart failure or a cerebrovascular catastrophe are not uncommon sequelae There is some evidence that hypertension is most marked during the active phase of the disease the blood pressure returning towards normal as the pituitary stimulus recedes If there is progression to failure of pituitary function then hypotension may be found.

(B) Associated Endocrine Disturbances

Diabetes mellitus complicates acromegaly in about one third of cases Its onset is by no means confined to the period of most intensive growth and it continues long after the acromegalic process has become static The response of the diabetes to insulin is as variable as in diabetes mellitus without acromegaly some patients exhibiting marked insulin resistance others a normal sensitivity It appears that the diabetogenic effect of growth hormone in the human is dependent on the capacity of the pancreas to secrete increased amounts of insulin Active acromegaly in the absence of diabetes suggests a high level of pancreatic function while transient diabetes disappearing as the growth stimulus stops indicates a failure to produce a peak level of insulin. Permanent diabetes in the absence of active growth is consistent with irreversible damage to the islet cells following a phase of increased activity Once established the course of diabetes and its treatment do not differ from that of other types of the disease

Hypogonadism is commonly an early feature of acromegaly probably due to an inhibition of gonadotrophin output as the pituitary is compressed by the eosinophil tumour Impotence in the male and amenorrhoea in the female are very frequent occurrences at the onset of acromegaly Occasionally if the pituitary tumour is unusually large testicular atrophy and loss of body hair is observed Following treatment or with spontaneous regression of the pituitary lesion a return to normal sex function is usual Successful pregnancies have been recorded in treated acromegalics However loss of libido may persist despite an

pure form of the disease which affects both sexes can only arise in adult life usually before the age of 50 years The mixed form of gigantism and acromegaly has been described in the preceding paragraphs The clinical picture of the disease has three facets the general effect of growth hormone associated endocrine disturbances and the local disturbances from the pituitary tumour (an adenoma composed of acidophil cells)

(A) Growth Hormone Effects

There is an insidious and progressive change in body form affecting both skeleton and soft tissue The skeletal changes are most obvious in the skull and extremities Enlargement of the lower jaw leads to marked prognathism and the teeth become separated from each other In the edentulous dentures no longer fit the jaw and become unusable The supra-orbital ridges are thickened and the prominence of this area is further marked by enlargement of the frontal sinuses Below the eye the zygomatic arches are thickened At the back of the skull thickening of the occipital protuberance occurs The long bones show little change but periosteal thickening may be noted and exostoses arise at the insertion of muscles The phalanges of fingers and toes become thickened with tufting at the end of the bone In contrast to these hypertrophic changes the spine becomes osteoporotic sometimes to a severe degree When the disease has been present for years hypertrophic osteoarthritis involves many joints and causes considerable disability Activity of the disease does not control the development of the arthritis

The most obvious soft tissue change is visible in the skin which is thickened coarse in texture greasy to touch and often rather hirsute Its overgrowth creates folds at the back of the neck like the scalp of a bull-dog The forehead is furrowed and the nasolabial folds are exaggerated leading down to thickened lips Over the hands the redundant skin leads to abnormal breadth and a spatulate appearance The underlying bony changes of skull and fingers accentuate the soft tissue growth to give the diagnostic appearance of the disease In some patients bony changes predominate in others these are less marked than the soft tissue abnormalities

Other organs are involved in the abnormal growth process Enlargement of the tongue with overgrowth of the papillae and hypertrophy of the vocal cords combine to produce a characteristically deep gruff voice with some difficulty of articulation Muscle mass may be obviously increased but although in the active phase of the disease there may be

considerable strength it is a common finding that muscle power is not as great as the bulk would suggest

The viscera are enlarged but liver and spleen are not palpable There may be enlargement of the heart either with or without hypertension Occasionally enormous hypertrophy of the myocardium occurs with a normal blood pressure but with electrocardiographic changes suggesting ischaemia Hypertension is probably more common in acromegalics than in the population as a whole It may be severe in degree and associated with papilloedema Heart failure or a cerebrovascular catastrophe are not uncommon sequelae There is some evidence that hypertension is most marked during the active phase of the disease the blood pressure returning towards normal as the pituitary stimulus recedes If there is progression to failure of pituitary function then hypotension may be found

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apparently normal gonadal system Under these circumstances it is probable that emotional rather than physical factors are the cause for it is usually associated with neurotic manifestations

There are rare instances of *pituitary tumours of mixed cytology which* are associated with acromegaly and Cushing s syndrome Other cases of acromegaly may show acne and hirsutes suggestive of adrenal overactivity in terms of androgen rather than the glucocorticoid production as in Cushing s syndrome Thyrotoxicosis has also been described in association with acromegaly but such cases are more rare than some authors suggest as a non-toxic goitre with a metabolic rate raised by the acromegalic process has led to the mistaken diagnosis of hyperthyroidism

A palpable enlarged thyroid is found in about 10 per cent of acromegalics Radio-iodine studies have indicated that thyroid function is normal The goitre is not always diffuse and may contain an adenoma, which is of particular interest in that adenomata of parathyroid islets of Langerhans and adrenal cortex are also described This disturbance of glandular structure is probably due to excessive growth hormone and not related to any functional disturbance of the affected glands

(C) Local Effects of the Tumour

Headache involving the whole of the head is an early and often distressing symptom Its relationship to the tumour is obscure as the pain may persist when treatment has diminished the size of the growth The most important evidence of an expanding tumour is the finding of visual defects due to pressure on the optic chiasma Enlargement of the blind spot and loss of red vision is followed by bi-temporal hemianopia Papilloedema is very rare but optic atrophy may occur at a late stage

Course of the Disease

The onset is very insidious so much so that gross distortion of the face can occur without the patient s realization The necessity for bigger gloves and shoes is usually the first point the patient notices Headache undue fatigue and loss of libido are the chief complaints

Without treatment the disease becomes inactive after a few years *No further overgrowth occurs* the patient s disfigurement *remaining constant* This stage commonly continues until the end of the patient s life Death is often unconnected with the acromegaly but hypertension or diabetes are potentially fatal complications of the disease Despite arrest of the disease it is common to find that a number of symptoms persist Headache and paraesthesiae of the limbs a feeling of exhaustion and

inability to concentrate make it difficult for the patient to work Osteoporosis of the spine and osteoarthritic changes in the joints combine to diminish the patient s mobility It is difficult to decide how many symptoms are due to endocrine dysfunction and how many to mental disturbance On the one hand evidence of hypogonadism is usually present in these patients who complain constantly of asthenia on the other hand substitution therapy with the appropriate sex hormones does not alleviate the symptoms in all cases Some patients show definite psychotic changes in behaviour

Failure of anterior pituitary function is a rare complication of acromegaly arising when the tumour after destroying the rest of the gland undergoes degeneration The resulting clinical picture is similar to panhypopituitarism arising from other causes The asthenic symptoms described in the preceding paragraph raise the suspicion of hypopituitarism but it is seldom that clinical examination and investigation confirm the diagnosis

Visual defects depend entirely on the size of the tumour and are not related to endocrine dysfunction or the general progress of the disease Hence the changes in vision must be assessed quite separately from the rest of the disease Once the disease has become static the tumour does not increase in size and therefore the visual defects will not change Sudden haemorrhage into the tumour provides an exception to this rule

DIAGNOSIS

Acromegaly is diagnosed on sight. If symptoms precede any gross alteration in structure diagnosis is more difficult but the demonstration of an enlarged sella turcica and a comparison of the patient s appearance with previous photographs are likely to resolve the problem Occasionally the thickened skin of myxoedema is at first glance reminiscent of acromegaly but the texture of the skin and the lack of skeletal changes will dispel any confusion Of greater importance is the normal individual whose facial features are suggestive of acromegaly In these cases the absence of change in features the presence of other members of the family with the same type of face and a normal sella turcica demonstrate the normality of the patient

However easy the initial diagnosis the insidious nature of the disease makes it difficult to assess the activity of the process If the patient gives a convincing story of changing features and enlarging extremities up to the time of examination it is safe to assume that the disease is active When this evidence is doubtful careful photography of the face and X-ray

of the skull will be invaluable for comparison with similar photographs made after an interval of a few months There is no test which gives direct evidence of excessive circulating growth hormone and the only chemical aid is affected by other metabolic processes This aid is the serum phosphorus level which is raised in active acromegaly Repeated estimations of phosphorus (as phosphate) are of some value in assessing the activity of the disease especially as the level will return to normal after successful treatment Phosphatase determinations are not of value

Apart from the investigations already detailed it is essential to plot the patient s visual fields and to repeat the measurement at regular intervals A glucose tolerance test should be performed when the diagnosis is first made and this too should be repeated at intervals

TREATMENT

Two facets of the disease require treatment firstly the production of growth hormone must be inhibited secondly the eyesight must be preserved The disfigurement and visceral changes of prolonged active acromegaly are such that early treatment is indicated in all cases where there is any suggestion of progressive disease Of course in the late stage of the disease where it is quite clear that the pituitary is no longer over active there is no indication for measures designed to suppress pituitary activity

The most effective method of inhibiting growth hormone secretion is deep X-ray therapy to the pituitary The dose required (about 1500 to 4000 r) is not likely to cause total pituitary failure The few cases who fail to respond will require surgical removal of the pituitary adenoma if the amount of radiation already received is the maximum that brain tissue can tolerate An ancillary method applicable to women is the administration of oestrogens which appear to have some general suppressive effect on the pituitary Menstrual irregularities or post menopausal bleeding may complicate this treatment Administration of oestrogen (say Stilboestrol 5 mg daily) only in the first three weeks of each menstrual cycle will diminish this risk

The place of surgery in treatment lies entirely in the preservation of vision A tumour which has failed to regress after deep X-ray therapy may threaten the patient with blindness Under these conditions surgical removal of the part of the tumour which involves the optic chiasma must be undertaken But a trial of X-ray therapy should always precede the hazard of surgical intervention

Diabetes mellitus will necessitate dietary treatment and probably

insulin. Its treatment is in no way different from that of idiopathic diabetes Hypogonadism must be treated with the appropriate sex hormone The necessity for such treatment is rare in females but common in males

Dwarfism

A dwarf is a person whose height is markedly below the limits of normal for his race It is reasonable to recognize a gradation from the dwarf to the patient of small stature whose departure from normality is not gross. So many factors are concerned in the production of dwarfism that true pituitary dwarfism due to an absence of growth hormone is a rare entity Consequently the whole subject of dwarfism will be discussed in its wider aspects before describing the pituitary type

The full height of a person is determined primarily on a genetic basis There are wide differences in racial and familial genetic constitutions The natives of Lake Chad have an average height of 6 feet 4 inches in striking comparison to the tribes of pygmies Less startling differences are seen in families The body will not reach the full stature of which it is capable from its genetic inheritance unless there is good health in the full sense of the phrase. Freedom from chronic infections and an optimum diet properly utilized are necessary factors As the average diet of school children in this country has improved over the years so has the average height of children increased from one generation to another

The endocrine system affects growth in three ways Growth hormone gives an overall stimulus to protein anabolism, probably aided by the effect of insulin in controlling the utilization of food Thyroid hormone determines the rate of metabolism and also the rate of body maturation (including the development of the epiphyses) Finally sex hormones particularly androgens which are present in both sexes cause increased somatic growth, and determine eventual height by closure of the epiphyses

A more detailed analysis of factors affecting growth is given on page 28 in a general classification of the causes of dwarfism It will be apparent that the majority of dwarfs do not suffer from primary endocrine disease and that the problem of diagnosis is one of general medicine

Pituitary Dwarfism

A pituitary origin for dwarfism is obvious if there is a demonstrable lesion of the sella turcica or if associated failure of adrenals thyroid and gonads indicates panhypopituitarism. However such cases are rare and in practice the diagnosis is made by inference after exclusion of other causes

CAUSES OF DWARFISM OR SMALL STATURE

Aetiology	*Type*	*Remarks*
1 *Genetic*	Hereditary small stature	Often a family history of short stature
2 *Nutritional*		
(a) Deficient intake		Food fads with emotional disturbances. A common type of short stature
(b) Deficient absorption	Steatorrhoea of all types	
3 *Endogenous Metabolic Disturbances*		
(a) Diabetes mellitus		Often associated with low caloric intake from too strict a diet
(b) Anoxia	Cyanotic congenital heart disease Chronic anaemia	
(c) Chronic renal failure	of all types	
(d) Hepatic failure	Cirrhosis	
(e) Inborn errors of metabolism		Fanconi's syndrome Glycogen Storage Disease etc
4 *Skeletal Disease*		
(a) Congenital	Achondroplasia Osteo-chondrodystrophies Osteogenesis imperfecta	
(b) Acquired	Rickets Tuberculosis	
5 *Chronic Infection*	Syphilis Tuberculosis	
6 *Rare Syndromes of uncertain aetiology*		
(a) Laurence-Moon-Biedl syndrome		
(b) Ulrick Turner's syndrome	(gonadal agenesis)	Small stature probably some genetic defect
(c) Progeria		
(d) Mongolism		
7 *Primary Endocrine Disease*		
(a) Lack of Pituitary growth hormone	(1) Pituitary dwarf (2) Dwarfism with sexual infantilism (3) Dwarfism with panhypopituitarism	No associated endocrine lesion
(b) Hypothyroidism	(1) Cretins Sporadic and endemic (2) Juvenile myxoedema	
(c) Cushing's syndrome		Inhibition of protein anabolism
(d) Precocious sexual development		Early closure of epiphyses Obvious in early adult life
(e) Failure of gonadal development		Obvious at age of puberty only

The birth weight and early development of the pituitary dwarf is normal but at the age of 5 to 6 years it becomes apparent that the rate of growth is no longer normal This slowing of the growth rate becomes more obvious as the years go by Normal sexual development is exceedingly rare in these cases so that infantilism (small stature with failure of sexual development) is found from the age of 15 years The patients bear a striking resemblance to each other Their bodies are perfectly proportionate but very lightly built The delicacy of their features is enhanced by a fine soft skin giving the impression of a Dresden china figure A normal intelligence and often a sweet temper match their petite fragile appearance This type of infantilism has been called the Loraine-Levi syndrome but as Loraine put his name to a paper describing infantilism associated with tuberculosis it is wise to adopt the term primary pituitary infantilism

Diagnosis

The majority of diseases that give rise to dwarfism are obvious from their various manifestations Confusion can arise between pituitary dwarfism genetic small stature and nutritional disorders Small stature from genetic origin may be distinguished by the fact that the child is small from birth the condition runs in the family and X-rays reveal no disparity between chronological and bone age Inadequate food intake due to refusal to eat or food fads is a common cause of small stature rather than dwarfism The diagnosis will be missed unless an adequate dietary history is taken in all cases Similarly cryptic steatorrhoea or chronic anaemia must be considered with the appropriate investigations if there is any history of bowel disturbance or pallor Moreover these diseases lead to delayed puberty with retardation of bone age in a manner very similar to primary pituitary infantilism Indeed it is probable that there is suppression of pituitary growth and gonadotrophic function caused by these defects of nutrition The point is clear that a primary lesion must not be diagnosed until these other diseases have been considered and excluded. Lastly gonadal agenesis with short stature may be confused with pituitary dwarfism but the presence of multiple congenital abnormalities short stature rather than dwarfism and only slight delay in bone ageing make the correct diagnosis possible

Treatment

At the present time there is no reliably potent preparation of growth hormone for clinical use Consequently treatment must be directed at

improving nutritional status and correcting gonadal insufficiency The employment of chorionic gonadotrophin or of the appropriate sex hormone will lead to a marked increase in somatic growth but has serious disadvantages Testosterone is the most potent steroid growth stimulator but it will cause virilism in girls marked sexual development in boys and early closure of the epiphyses Therefore it should be used in boys only after the age of twelve years Chorionic gonadotrophin produces a slight growth response which is proportional to the degree of testicular activity induced it has little effect on girls It may be used just prior to the normal age for puberty Oestrogens cause sex development with a growth spurt which is not so marked as that produced by androgens Dosage and route of administration for these hormones are discussed in the section on hypogonadism (pages 145 and 156)

Steroids with minimal sex effect but some protein anabolic action may be used but are rather disappointing in practice Androstene-diol is a suitable preparation in doses of 20-50 mg daily

Any steroid treatment must be adjusted so that sex development is not greatly in excess of somatic growth and serial X-rays of epiphyses are necessary to guard against premature closure with its abrupt termination of growth

It is a wise policy to withhold endocrine therapy in the child while concentrating on an optimum diet By this policy of watching and repeated assessment the growth rate may be observed

Panhypopituitarism (Anterior Pituitary Failure)

Destruction of the anterior pituitary with a loss of its secretory function is followed by a functional failure of the glands under pituitary control The resultant syndrome was described by Simmonds who introduced the unfortunate term Pituitary Cachexia Consequently it was considered that emaciation was a major feature of panhypopituitarism a misconception finally dispelled by Sheehan who not only clarified the clinical picture but the aetiology of the disease

It has been estimated that about nine tenths of the anterior pituitary must be put out of action before signs of failure appear Of course a tumour may disturb function by pressure without gross destruction of the gland The syndrome not only varies in severity but also in the degree to which any one target gland is affected In general damage to the pituitary affects first gonadotrophin and growth hormone production and then the life-maintaining trophic hormones related to the adrenal cortex and thyroid The metabolic disturbance may be complicated further if

the causative lesion involves the hypothalamus Panhypopituitarism is more common in females because of its association with post partum haemorrhage while space-filling lesions are the most common cause in men The variety of lesions responsible for the disease is listed below

(1) *Ischaemic Necrosis*

Ischaemic necrosis occurs after an abrupt cessation of normal blood flow The highly vascular state of the pituitary during pregnancy and the gross drop in blood pressure with obstetric shock explains why the most common antecedent to this lesion is severe post-partum haemorrhage Puerperal sepsis does not cause the lesion.

In women ischaemic necrosis is the most common cause of panhypopituitarism. Almost complete destruction of the pituitary can occur with severe endocrine disturbance On the other hand when destruction is not so complete some degree of functional recovery may be seen

(2) *Tumours*

A wide variety of neoplasm both primary and secondary may involve the pituitary At the same time the hypothalamus may be involved so that the clinical picture becomes a mixture of hypothalamic and pituitary dysfunction Neurological abnormalities may dominate the syndrome as complete destruction of the pituitary is not common

The important non-functioning pituitary tumour is the chromophobe adenoma This benign growth is very rare before the age of 20 and is usually seen in the fourth and fifth decades affecting both sexes Upward extension with involvement of the optic chiasma occurs early so that the patient presents with headache and visual field defects rather than with endocrine symptoms An increase in weight is also a characteristic early symptom suggesting a hypothalamic disorder Gross panhypopituitarism is rare but may arise after operative removal of the tumour

The craniopharyngioma (Rathke pouch tumour) is the other important space-filling lesion of pituitary origin but it is not a true neoplasm, arising as it does as a cyst in the embryonic remnants of Rathke s pouch. Its usual situation is above the diaphragma sellae so that hypothalamic disorders may occur but in some cases there is considerable intrasellar expansion with very severe panhypopituitarism It arises before the age of 20 and is the only common space-filling lesion to affect the pituitary in the first two decades of life

(3) *Fibrosis*

Subacute or chronic fibrotic lesions of uncertain aetiology are not unusual Fibrosis may of course represent the final stage of various patho logical processes such as ischaemic necrosis The degree of glandular disturbance may be so severe that at autopsy the sella turcica appears to be empty

(4) *Granulomata*

These are rare causes of panhypopituitarism but both syphilis and tuberculosis can cause destruction of the gland Both conditions must be considered if the disease arises in the absence of a demonstrable tumour or history of post-partum shock A curious condition of uncertain aetiology is the giant cell granuloma which may affect other glands apart from the pituitary

(5) *Trauma*

Head injury is very rarely followed by anterior pituitary failure but surgical procedures involving the gland may lead to complete pituitary destruction and are sometimes designed to do so

CLINICAL COURSE

The clinical picture is determined by the presence or absence of a space-filling lesion with attendant neurological abnormalities the possibility of hypothalamic involvement and the age of the patient Obesity suggests hypothalamic damage while diabetes insipidus confirms it It must be remembered that severe anterior pituitary failure may mask diabetes insipidus in that the polyuria is only slight and the urine specific gravity not so low This is due to the associated adrenocortical failure Treatment with A C T H or cortisone is followed by the full polyuria and low specific gravity of a frank diabetes insipidus The age of the patient determines growth and sexual disorders Dwarfism is only apparent if the lesion occurs in childhood and sexual infantilism is present if the disturbance arises before or during puberty In the elderly hypogonadism is difficult to evaluate

Perhaps the most uncomplicated form of the syndrome is seen after ischaemic necrosis of the gland because there are no neurological abnormalities and no damage to the hypothalamus The lesion is acute in onset but chronic in its course so that a description of the clinical picture which results will be the best account of pure panhypopituitarism

After recovery from the initial obstetric shock the first sign of an endo-

crine disturbance is failure to lactate Convalescence is prolonged weakness and lassitude persisting During this stage it may be noted that the pubic hair shaved prior to labour is growing very slowly As the months go by the patient shows no signs of returning to normal activity Muscular weakness and excessive fatigue are coupled with a marked lethargy which restricts daily routine and may abolish normal life There is a tendency to faintness on standing and dizziness perhaps with some mental confusion on fasting Any infection is poorly tolerated with an exaggeration of the fatigue and weakness

The nutritional state remains good as emaciation is not characteristic of the disease An initial loss of weight if puerperal sepsis is present is not followed by further wasting Indeed there may be some weight gain in those cases which are predominantly hypothyroid Failure to recognize this point has been the main reason for missing the diagnosis of panhypopituitarism

Another characteristic feature is an intense feeling of cold even in a temperate environment The patient is chilled to the bone and huddles close to the fire This symptom is so marked that it is often volunteered by the patient at an early stage in the history taking

Amenorrhoea persists from the onset of the lesion. Very occasionally an irregular scanty menstrual loss occurs at long intervals Atrophy of the genital tract leads to pain on coitus while complete loss of libido is the rule

Once established the disease pursues a prolonged course liable to abrupt termination in adrenal or hypothyroid crisis but usually lasting for many years It is not uncommon to find a patient grossly disabled by the disease who has survived twenty or more years without treatment But the hold on life is precarious at all times and in the late stages the patient is reduced to a twilight existence more vegetable than human

PHYSICAL SIGNS

The underlying disorders of function are a combination of hypogonadism hypothyroidism and adrenocortical insufficiency The general appearance of the patient suggests myxoedema from the thin scalp hair scanty eyebrows puffy eyelids and face and the monotonous low voice But the skin texture is very fine and soft with a uniform pallor which is often extreme Definite wrinkling around the eyes contrasts with the soft hairless skin to make a curious mixture of youth and age from which the actual years of the patient cannot be deduced Body hair is absent or very sparse and the axillae free from sweat Some pallor of the mucosae

is the rule but the skin pallor is always more marked the only pigmentation seen is on the legs from erythema ab igne a confirmation of the patient s complaint of cold

The vulva and lower genital tract is atrophic and the uterus often minute Atrophy of the breasts is seldom obvious clinically

Cardiovascular abnormality may be indicated by a slow regular pulse and a degree of hypotension more marked on standing There is nothing remarkable about the nutritional state of the patient At a late stage emaciation may stem from anorexia but it is indicative of the stage of the disease and not of the diagnosis

OTHER FORMS OF PANHYPOPITUITARISM

When the disorder arises in childhood or adolescence the predominant endocrine features will be dwarfism and sexual infantilism It is unusual to see gross clinical evidence of adrenal and thyroid insufficiency in these young patients

The partial destruction of the pituitary by a chromophobe adenoma presents a picture of hypogonadism with the fine hairless skin of panhypopituitarism and a moderate obesity

In some cases hypothyroidism is the dominant feature the whole picture closely resembling myxoedema except for the fine skin and gross loss of body hair

COMPLICATIONS

Psychosis

In the later stages of the disease mental apathy passes on to a psychotic depression or severe mental confusion and disorientation It must be remembered that both Addison s disease and myxoedema precipitate psychotic changes so that it is not surprising to find the patient with panhypopituitarism developing mental disorders which may necessitate institutional care Occasionally frank psychosis becomes obvious for the first time when treatment has been instituted and the original apathy dissipated Acute mania with delusions is common under these conditions

Pregnancy

This is not so much a complication as an indication of partial recovery which has enabled conception to take place Cases have been described where complete cure of the condition has followed the pregnancy Of course such a recovery may have occurred just prior to conception However some go through pregnancy in a good state of health only to

relapse quite severely in the puerperium A further important point arises in those patients who have developed the disease after a post-partum haemorrhage Subsequent pregnancy may be followed by another post partum haemorrhage recurrent retention of placenta is the usual cause This possibility must be anticipated and necessary precautions taken.

Acute Crises

A crisis may be the terminal breakdown of the patient s adjustment to the disease or be precipitated by infection or trauma Any operation in the region of the pituitary can cause such a crisis and the possibility should be considered in the diagnosis of any disturbance of consciousness following surgery of this type Clouding of consciousness drowsiness and withdrawal from reality are indeed symptoms common to all types of crisis whatever the precipitating factor Three types of crisis can be recognized according to the predominant disorder of function although features of each type may be present at the same time

(*a*) *Electrolyte Crisis*

Salt depletion from excessive urinary loss with potassium retention arising from adrenocortical insufficiency (in terms of mineralocorticoids) Dehydration extreme muscular weakness and hypotension are found As in Addisonian crisis anorexia is followed by vomiting which exaggerates the dehydration yet the urinary chloride remains normal or high

(*b*) *Hypoglycaemic Crisis*

Dramatic falls in blood-sugar accentuated by fasting are due to insufficient adrenal glucocorticoids Drowsiness and apathy give way to complete confusion often with excitement which ends in convulsive movements akin to epilepsy A less obvious clinical picture due to the same lack of cortisone-like steroids is gradually increasing fatigue associated with extreme anorexia Generalized aches and pains often accompany the feeling of lassitude while the patient ceases to take an interest in his surroundings and his emotional reactions may be bizarre In this type of crisis the blood pressure is usually normal and dehydration does not occur

(*c*) *Hypothermic Crisis*

This is predominantly due to hypothyroidism and is similar to the crisis of myxoedema However adrenal insufficiency is always present and will be exacerbated if treatment is by means of thyroid extract only The onset is gradual the patient slowly sinking into a vegetable state both

mentally and physically The body temperature slowly falls and as it does so the patient passes from stupor to deep coma with a marked bradycardia and hypotension At the end the corpse-like body shows a spark of life solely by occasional respiration This form of crisis has been termed with some accuracy a hibernation coma

DIAGNOSIS

Multiple glandular deficiencies must be demonstrated to suggest the diagnosis while visual field defects and the radiological appearances of an expanded or destroyed sella turcica confirm the disorder of function and indicate the aetiology It is important to seek for a history of post-partum haemorrhage and for evidence such as the giving of a blood transfusion which will support the patient s story Only severe post-partum haemorrhage will be followed by pituitary necrosis and in many cases alarming haemorrhage does not lead to any subsequent pituitary disorder The common difficulties in diagnosis arise with the following disorders

NON-ENDOCRINE CONDITIONS

Persistent Anaemia

A patient with a haemoglobin of 60-75 per cent yet with extreme pallor and symptoms of a greater severity than the anaemia is likely to cause is possibly suffering from hypopituitarism In all normochromic anaemias which fail to respond to treatment the question of endocrine disturbance should be considered On the other hand a number of patients suffer from anaemia after post-partum haemorrhage with complaints of weakness and fatigue yet have not pituitary insufficiency Rapid reponse of the haemoglobin and symptoms to haematinics will dispel any doubt as to the diagnosis Normal body hair lactation and menstruation will exclude panhypopituitarism

Neurosis — Nervous Debility

Such conditions are common while panhypopituitarism is rare so that on many occasions the physical appearance of panhypopituitarism goes unrecognized and the patient is labelled a neurotic because of constant fatigue and depression. If frank psychosis occurs its endocrine origin may not be realized

A word must be said on anorexia nervosa if only because it used to be considered that the emaciation characteristic of the condition was also seen in panhypopituitarism.

The rarity of emaciation in pituitary insufficiency has been made clear already Anorexia nervosa as the name implies is a state of starvation following complete loss of appetite of psychic origin The condition is often hysterical in nature but may be due to more severe mental illness It is most common in young unmarried women Amenorrhoea is an early symptom occurring before there is gross loss of weight. Absolute refusal of food leads to extreme emaciation reminiscent of a concentration camp yet the patient is still active and not unduly fatigued Indeed compulsive activities may be a feature of the disturbance In contrast to the hairless fine skin of panhypopituitarism there is a covering of fine downy hair over a dry rather coarse body skin The only confusing point in diagnosis is the fact that long standing starvation gives rise to a functional depression of the pituitary Therefore the history and physical examination of the patient are more reliable than tests of pituitary function

Endocrine Conditions

Myxoedema

Many cases of panhypopituitarism present with hypothyroidism as the dominant feature The puffy face slow hoarse voice and sensitivity to cold are common to both forms of hypothyroidism But the texture and colour of the skin is very different for in myxoedema the skin has a yellowy tinge with red patches on the cheeks and a coarse rough feel Moreover loss of scalp hair and eyebrows is more marked than thinning of body hair while the reverse holds true for panhypopituitarism. Clinical evidence of adrenal insufficiency is absent and severe hypogonadism does not occur in myxoedema although there may be chemical evidence of hypofunction of these glands If such tests give equivocal results a short course of thyroid therapy (only a small dose should be used) will be followed by a return to normal values for the tests if the patient has myxoedema It should be remembered that the clinical response to thyroid therapy is more definite in primary myxoedema than in panhypopituitarism

Addison s Disease

Pigmentation of skin and mucous membranes is characteristic of Addison s disease while lack of pigmentation is typical of panhypopituitarism This is a fundamental distinction between the two diseases Confusion may arise if it is not realized that loss of body hair is common in women with Addison s disease and that some intolerance to cold may be a minor symptom

AIDS TO DIAGNOSIS

Two lines of investigation are required the first to confirm the disorder of function the second to discover the aetiology of the lesion The most useful tests of function are those concerned with the thyroid and adrenal (see Appendix) In particular failure to eliminate a water load and the response to induced hypoglycaemia are valuable although the latter test is not without danger A very low level of ketosteroid excretion is found in both sexes and a four-day course of A C T H will raise this level indicating that the adrenal is intact Similar techniques of stimulation are being developed as tests of thyroid function, utilizing the uptake of radio-iodine to the gland before and after the administration of T S H The only *direct assay of pituitary hormones which is available at present* is the determination of urinary gonadotrophins However techniques suitable for the determination of very small amounts of gonadotrophin are not entirely satisfactory and the assay is not widely available

The aetiology of the lesion may remain unknown unless a space occupying lesion of the pituitary is present or there is a good history of severe post-partum haemorrhage An X-ray of the skull with a special view of the sella turcica is an essential investigation A Wasserman reaction should not be forgotten if the aetiology is obscure

TREATMENT

Physiological replacement therapy by means of an anterior pituitary *extract is not a practical proposition and treatment is therefore dependent* on the correction of various aspects of the disorder The hormones required are listed in the order of practical importance

(1) *Cortisone*

Maintenance of adrenal function or adequate substitution for it is the most important aspect of treatment The convenience of oral administration makes cortisone the hormone of choice It is particularly valuable as glucocorticoid rather than mineralocorticoid activity is required in pan-hypopituitarism If necessary extra salt can be given and very rarely indeed will such salt retaining hormones as deoxycorticosterone be needed as additional therapy An adequate dose of cortisone ranges from 12 5 mg to 50 mg per day in the absence of incidental infections or trauma It is wise to administer the hormone at least twice daily the doses being spaced evenly

The only complication of this treatment is the exacerbation of a latent psychosis in long standing cases Frank mania may result unless small doses are used initially and the mental state most carefully assessed at the outset

(2) *A C T H*

It is logical to restore normal stimulation of the adrenal by A C T H It is ideal as initial treatment but if the disease is of long duration the adrenal response will be slower than normal so A C T H is not a suitable emergency treatment in the previously untreated case Long term treatment necessitates repeated injection although the number can be reduced to one or two a week by using A C T H gel

(3) *Sex Hormones*

In distinction from its sex effects the protein anabolic action of testosterone has proved of great value in the treatment of either sex It improves muscular power resistance to fatigue and general well-being Virilization of female patients is very uncommon at the dosage required Methyl testosterone 10-20 mg daily or implants of pellets of testosterone from 200-400 mg every six months are suitable regimes

The greater efficiency of cortisone in general treatment is bringing testosterone back to its role as a sex hormone for male patients only Cortisone will often restore libido but does not influence potency Therefore androgens are required for restoration of normal penile erection and volume of ejaculate The route and type of administration is similar to that for hypogonadism (see Chapter IX)

In the female the indication for the use of oestrogens is the atrophy of the lower genital tract rather than amenorrhoea Unless the patient is seriously disturbed by her lack of menstruation, production of an oestrogenic withdrawal bleed is a doubtful luxury However atrophy of the vaginal mucosa causes dyspareunia which is cured by oestrogen therapy Small doses of oestrogen (i e stilboestrol 0 5 mg daily) may be sufficient and can be given continuously If larger doses are required it is wise to give cyclical therapy three weeks of oestrogen daily followed by one week without treatment By repeating this course month by month withdrawal bleeding (in this instance a justified necessity) will occur in the week without tablets thus avoiding the possibility of severe haemorrhage which can occur after prolonged continuous oestrogen therapy

Progesterone (or ethisterone) has no practical application in the treatment of panhypopituitarism

(4) *Thyroid Extract*

An increase in the metabolic rate when the adrenals are in a state of hypofunction may precipitate acute adrenal insufficiency For this reason thyroid should not be used as the only mode of therapy But in many cases hypothyroidism is the dominant aspect of the disorder so

that thyroid is essential for successful treatment Provided that cortisone or testosterone is given simultaneously an initial dose of thyroid gr 1 daily is safe After two or three weeks this dose can be doubled if considered necessary and after a *further interval of three weeks it is safe* to pass to a maximum of gr 3 daily Larger doses than this are not required

Treatment in Special Circumstances

Operations involving the pituitary

Surgery in this area may cause temporary or permanent damage to the pituitary particularly if the gland itself is diseased Deliberate removal of a normal pituitary is sometimes carried out for the amelioration of carcinomatosis (from a primary in breast or prostate) or severe hypertension Immediate post-operative pituitary failure may be avoided by the administration of A C T H 60–80 mg daily given in six-hourly intramuscular injections and started at least two days prior to operation This dose is continued until the fifth or sixth day post-operatively and then reduced by 50 per cent each day so that the effect is gradually diminished rather than stopped abruptly During the operative period it is not necessary to give extra salt so the normal daily requirements (5–8 grms) should be given *The initial administration will be intravenous and 5 per cent* dextrose with ½ normal saline is preferable to normal saline

Any disturbance of consciousness after the operation suggests uncontrolled hypopituitarism if traumatic causes can be excluded Increasing lethargy proceeding to coma or gross anorexia with vague aches and pains is very suggestive of pituitary insufficiency The response to 100 mg of cortisone i m may be a diagnostic aid

Treatment of Crises

Treatment of a crisis is directed towards the cause of the collapse usually an infection and the rapid restoration of the level of circulating *glucocorticoids In the absence of demonstrable infection it is* a wise precaution to start penicillin as a safety measure The most effective hormone therapy is hydrocortisone 50 mg in alcohol given rapidly via an intravenous infusion of 5 per cent dextrose At the same time intramuscular cortisone 100 mg should be given so that its absorption will be effective by the time the initial intravenous therapy is discontinued Repeated intramuscular injections of 100 mg cortisone every 8 or 12 hours will be necessary until the crisis is over The response of the adrenal to A C T H is too slow under these circumstances to warrant its use Salt depletion is rare and satisfactorily dealt with by an infusion of 1/5

normal saline There is a danger of giving too much water at a time when water excretion is impaired Therefore intravenous therapy should be continued with caution the water and salt requirements being judged according to the loss in the urine Primarily mineralocorticoid preparations are not necessary

The treatment of hibernation coma is very difficult. Warming the patient by an electric cradle must be undertaken but the temperature should be raised very slowly indeed Intravenous hydrocortisone is the hormone of choice although the prognosis remains grave despite treatment The vexed problem is whether or not to administer thyroid for undoubtedly hypothyroidism is the dominant lesion. Massive thyroid therapy has been attempted but the wiser course is to give thyroxine in moderate dosage (0 1 mg orally twice daily) The quicker action of tri-iodothyronine is to be preferred and if available it should be given in doses of 0 02-0 04 mg twice daily The rarity of the condition does not allow as yet for any standard treatment

CHAPTER IV

THE THYROID

Anatomy

The shape of the thyroid resembles a butterfly the isthmus representing the body and the right and left lobes the wings The gland lies over the anterior and lateral aspects of the trachea The isthmus is about 4 mm thick and square in shape (about 20 × 20 mm) covering the anterior aspect of the trachea just below the cricoid The lobes are about 40 mm in length and about 25 mm antero-posteriorly with a thickness (lateral from the trachea) of 15-20 mm The upper part of the lobes are well demarcated reaching to the level of the thyroid cartilage

The thyroid is covered by a thin fibrous capsule which sends septa into the substance of the gland giving rise to an irregular lobulation of the surface The blood supply is abundant with many anastomoses Two pairs of arteries supply the gland the superior thyroid arteries from the external carotids and the inferior thyroid arteries from the subclavian artery The nerve supply does not appear to be of great clinical importance

The functional unit of the thyroid is the follicle which is roughly spherical with a mean diameter of about 300µ Its wall consists of a single layer of epithelial cells which synthesize thyroid hormone the shape of the cell varies with functional activity being cuboidal under normal conditions and columnar with hyperactivity The centre of the follicle is filled by colloid a protein substance in which the hormone is stored

The normal thyroid is just palpable provided the neck is thin The examiner should stand behind the patient using the fingers of both hands for palpation with the patient s neck held midway between flexion and extension The gland moves with deglutition and the patient will co-operate better if given some water to swallow

The Hormone

The thyroid *synthesizes its hormone from tyrosine and iodine* The steps leading to hormone secretion are as follows

(1) *Concentration of Iodide in the Gland*

The thyroid *is* capable of extracting iodide from the blood and maintaining a concentration of iodide that is many times above the blood concentration No other organ has this property (the salivary glands have a

weak iodide concentrating power) The capacity to concentrate iodide is distinct from the mechanisms by which iodide is converted to hormone

(2) *Combination of Iodide with Tyrosine*

It is most probable that di-iodotyrosine is the first product formed rather than mono-iodotyrosine

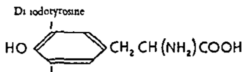
(3) *Conversion of Di-iodotyrosine to Thyroxine*

Two molecules of di-iodotyrosine are condensed to form a molecule containing four iodine atoms which is tetra iodothyronine or thyroxine Extracts of thyroid contain thyroxine in a racemic mixture but laevo thyroxine is 8-10 times more potent than the racemic mixture and is probably the form in which thyroxine is present in vivo

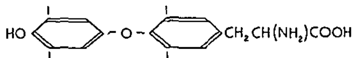
(4) *Storage of Thyroxine in Colloid*

Thyroxine is stored in the colloid of the thyroid vesicle in the form of thyroglobulin The molecular weight of this compound is too great to allow its passage into the blood stream

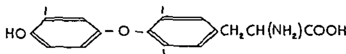
Di iodotyrosine



Tetra iodothyronine = Thyroxine



Tri iodothyronine



IODINATED COMPOUNDS RELATED TO THE THYROID

(5) *Release of Thyroxine into Circulation*

Thyroxine is detached from its loose combination with protein in the colloid and passes through the thyroid cells into the blood stream

(6) *Action of Thyroxine on Tissues*

Recent work makes it very probable that thyroxine which is the circulating thyroid hormone is not in itself the agent directly affecting the tissues The active agent appears to be tri-iodothyronine The necessary de-iodination occurs in the tissues and the activity of tri-iodothyronine is at least five times that of thyroxine Moreover its speed of action is quicker and the duration of its effect far shorter than thyroxine

CONTROL OF THYROID ACTIVITY

The principal controlling factor is T S H (thyrotrophic hormone) secreted by the anterior pituitary In terms of the hormone cycle its first action is to promote the release of thyroxine from the colloid into the blood stream Its second action is to increase the uptake of iodide which in turn leads to a higher rate of hormone synthesis Thus T S H raises the circulating level of hormone by depleting the store of hormone already formed and maintains the higher level by increasing the rate of synthesis By these mechanisms the passage of iodine through the thyroid is accelerated

Cytological changes accompany the functional alterations determined by T S H the amount of colloid diminishes and the cellular elements of the gland increase The cells of the vesicles change from cuboidal to columnar epithelium and hyperplasia follows so that papillary ingrowths fill the centre of the vesicle from which colloid has been removed

As already stated the degree of T S H stimulation depends on the feed-back mechanism a falling level of circulating thyroid hormone leading to an increased secretion of T S H and vice versa By this means a constant level of thyroid hormone is ensured but impulses from the cerebral cortex transmitted via the hypothalamus can alter the sensitivity of the feed-back control Others factor including the autonomic system do not appear to exert a direct influence on the thyroid

THE IODINE CYCLE

Immense strides in the knowledge of thyroid physiology have been made in recent years by the use of radio-active iodine Having emerged from the field of pure research isotopic iodine now makes important contributions to the diagnosis and treatment of thryoid disease For this reason the iodine cycle must be described

In a normal diet about 100-200 micrograms of iodine are consumed daily (in the form of iodides) The amount will be considerably greater in those who eat large quantities of fish and will also vary according to the iodine content of the drinking water Iodine is absorbed rapidly and

completely by the stomach and upper part of the small intestine On reaching the blood stream it diffuses into the extra-cellular fluid, taking about three hours to reach equilibrium. At this stage the tissue concentration of iodine will be directly proportional to the blood level.

Iodine circulating as iodide is removed from the bloodstream by two mechanisms firstly by thyroid trapping and secondly by renal excretion into the urine The rate of disappearance of iodine from the blood depend upon the efficiency of the thyroid and kidney Excretion in sweat and saliva plays a very small part in the elimination of the element

On entering the thyroid the iodine is rapidly combined with tyrosine to form thyroid hormone It remains in hormonal form stored in the colloid for many days probably for 2-3 weeks On discharge from the thyroid the iodine circulates as hormone passing through the liver entering the bile and being reabsorbed from the gut into the blood In the tissue the hormone is broken down so that iodide is released to start its cycle again.

THE ACTION OF THYROID HORMONE

The overall action of thyroid hormone is stimulation of the metabolic rate In the child it has an important effect on the maturation of tissues The relationship of hormonal action to the signs and symptoms of thyroid dysfunction can be indicated clearly in the following table

	DISORDER OF FUNCTION	
Site of Action	*Hyperactivity*	*Hypoactivity*
Metabolic rate (calorigenic action)	Weight loss Peripheral vasodilation Sweating hot skin	Weight gain Pale dry cold skin
Heart	Tachycardia (auricular fibrillation) Increased cardiac output High pulse pressure	Bradycardia Low cardiac output Low pulse pressure
Central Nervous System	Increased autonomic action Anxiety and labile emotions	Lethargy and stupor
Growth (1) Skeletal maturation (2) Cerebral maturation	Increased growth rate in children	Delayed growth Epiphyseal dysgenesis Mental retardation
Alimentary tract	Tendency to diarrhoea	Constipation
Bone marrow		Anaemia
Tissues		Myxoedemic infiltration of skin and fluid retention
Other metabolic processes (1) Cholesterol	(1) Decreased serum cholesterol	Increased serum cholesterol (high incidence of coronary artery disease)
(2) Calcium	(2) Osteoporosis	
Other Endocrines	Disturbed menstrual rhythm	Hypogonadism Adrenal function impaired

Goitre

The term goitre may be applied to any enlargement of the thyroid due to any lesion varying from lack of iodine to neoplasia Hence a label of goitre without qualification is of no diagnostic significance and merely alarms the patient All classifications of thyroid enlargement can be attacked by the purist because the variety of histological change is limited and the correlation with function is poor In practice the physiological abnormalities underlying the thyroid enlargement are the important element so that a classification based on these factors is that of greatest interest to the clinician

CLASSIFICATION OF THYROID ENLARGEMENTS

A *With normal hormone production*

1 Iodine lack
  (a) Endemic goitre
  (b) Sporadic non-toxic goitre (especially of puberty and pregnancy)

2 New Growths
  (a) Adenomata
  (b) Metastasising Tumours (also secondary neoplastic deposits involving thyroid)

3 Thyroiditis
  (a) *Hashimoto s Type (disorders of hormone production may occur)* Lymphadenoid goitre
  (b) Riedel s Type
  (c) Infective

B *With disordered hormone production*

1 Hypofunction
  (a) Goitrous Cretinism Endemic
  Sporadic
  (b) Administered goitrogens

2 Hyperfunction Thyrotoxicosis
  (a) *Arising simultaneously with thyroid enlargement*
  (b) Associated with previously non-toxic goitre
  (c) Arising in an adenoma

Endemic Goitre

In certain areas of the world many of the population are afflicted by a thyroid enlargement which may reach enormous proportions The com-

mon factor to all these areas is a deficiency of iodine in diet and drinking water

The relationship between iodine deficiency and thyroid enlargement was demonstrated clearly in Switzerland and elsewhere the percentage of the population with enlarged thyroids was found to be inversely proportional to the iodine concentration of the drinking water The introduction of iodised salt into the diet was followed by a dramatic decrease in the incidence of goitre

This early clinical work has been amply confirmed in the laboratory and by modern methods of clinical study in the Andes It is now apparent that factors other than iodine deficiency may be responsible for this type of goitre by interfering with the thyroid s utilization of available iodine Goitrogens in certain vegetables and variations in calcium and fluorine concentrations of drinking water have all been incriminated On withdrawal of iodine from the diet the thyroid undergoes compensatory hypertrophy under the influence of T S H The enlarged gland has a marked avidity for iodine for it is only by an increase in its efficiency to concentrate iodide that normal hormone production is possible in the presence of a low serum iodide level As hypertrophy continues the histology changes from the initial proliferation of cells to areas of atrophy in which the vesicles are distended with a poorly staining colloid and cellular elements become rare In the late stages when the gland has reached a very great size the whole structure consists of large colloid cysts this is the end result of alternating waves of hyperplasia and exhaustion atrophy

The world distribution of endemic goitre shows a predilection for mountainous areas In Europe the Alps Carpathians and Pyrenees in Asia the Himalayas and in America the Andes are all areas where goitre is prevalent But some non-mountainous districts such as the Great Lakes of Canada are affected the common denominator being deficiency of iodine in the water

In England there is no area where the population is affected severely but the incidence of goitre is comparatively high in an area extending from Cornwall north-eastwards through Somerset and between the Cotswold and Chiltern Hills into Northamptonshire Derbyshire and the Pennine chain Offshoots from this line extend through Wiltshire to the Isle of Wight over Hereford into South Wales and through Cheshire to North Wales The maximum incidence of goitre is in the Mendip Hills and in North Oxfordshire although tradition holds to the name Derbyshire neck for the goitre In all these areas rural rather than

urban populations are affected probably because of differences in diet and water supply

In any endemic area there is a correlation between the percentage of the population with goitre and the sex ratio of those affected If the incidence of goitre is very high men and women are affected equally As the incidence declines the ratio of women to men is increased This sensitivity of the female thyroid to mild iodine deficiency is probably related to the sex cycle the thyroid becoming enlarged in puberty and pregnancy presumably when the body s demand for iodine is increased Indeed the story is told of a village in a goitrous area where the bride has a silken cord tied round the neck at marriage The breaking of the cord by an enlarging thyroid is used as an early sign of pregnancy

Endemic goitres give rise to symptoms because of their size for they may be larger than any other type of thyroid enlargement Hormone production is usually adequate but in those areas of extreme iodine deficiency where goitre has been prevalent for generations goitrous mothers give birth to goitrous cretins with all the tragedy of mental defect that such hormone deficiency implies for the child There is also a curious association of endemic goitre with deaf mutism Lastly thyrotoxicosis may occur at a later date but there is no conclusive evidence that this disease reaches a higher incidence in areas of endemic goitre When iodination of the diet was introduced in Europe a few cases of thyrotoxicosis appeared to follow This unusual result of increasing the iodine intake is due to the gland being presented suddenly with sufficient iodine to manufacture hormone in a normal manner when its efficiency for hormone synthesis is at an abnormally high level Thus for a short while excessive amounts of hormone are produced No case of iodide induced thyrotoxicosis has been reported from the British Isles

Thyrotoxicosis

No really satisfactory name has been evolved for this disease Thyrotoxicosis toxic goitre exophthalmic goitre hyperthyroidism all indicate somewhat imperfectly the nature of the disturbance They have more value than the eponyms Graves s disease or Basedow s disease both of which have little historical value as the disease was described first by Parry

Aetiology

Thyrotoxicosis is a psychosomatic disorder The body disturbance is due predominantly to a continued excessive secretion of thyroid hor-

mone initiated in some obscure way by emotional factors Such events as puberty pregnancy or infection may precipitate the disease, but it is emotional stress that appears to be the most important agent. Patients who develop thyrotoxicosis are often highly strung over anxious and have insecure personalities But why some people respond to an adverse emotional environment by developing hyperthyroidism remains an unanswered question

Another factor is the variable degree to which the individual thyroid will respond to stimuli Thyrotoxicosis is of world wide distribution and does not follow the geographical incidence of endemic goitre Therefore race and iodine deficiency have no obvious effect on the sensitivity of the thyroid But there is a considerable sex difference as 80 per cent of thyrotoxics are female Such susceptibility may run in a family many cases of thyrotoxicosis occurring among the siblings

However none of these statements gives any clue to the basic aetiology of the disease *It may be said that psychic trauma and other activating* factors fire off thyrotoxicosis but no-one knows how the gun is loaded or how the trigger is pulled

PATHOLOGICAL PHYSIOLOGY

The stimulus from which thyrotoxicosis develops probably passes via the hypothalamus and anterior pituitary to reach the thyroid by the influence of T S H It would seem that the initial hyperthyroidism is stimulated by an excess of T S H but the role of the pituitary in maintaining excessive thyroid activity is uncertain The thyroid may become autonomous in its activity or remain dependent on the pituitary As yet there is no clear cut answer to this all important question

The changes in the structure of the thyroid are similar to those produced experimentally by continued stimulation with T S H The gland is enlarged diffusely with an increase in cellular elements Colloid material is conspicuous by its absence and the acini are filled with papillary ingrowths from the epithelium which is of high columnar type There is also a considerable increase in the blood supply the whole gland being highly vascular

Thyrotoxicosis may develop in a gland already goitrous so that the histological picture is a mixed one of past hyperplasia and atrophy together with new areas of hyperplasia Occasionally an adenoma becomes hyperactive but in most instances it is the surrounding gland that is overactive and the adenoma does not contribute to the excess hormone production

Studies of thyroid function by means of radio-iodine have demonstrated that the gland in thyrotoxicosis is avid for iodine There is an increase in the ability to concentrate iodine from the blood stream in the speed of conversion of iodine to hormone and the release of hormone into the circulation. The absence of colloid is histological confirmation of the rapid transit of the hormone and lack of storage The circulating hormone level varies with the severity of the disease but it is at least twice the normal value

It must be emphasized that there is no production of an abnormal hormone The circulating hormone is normal in quality but excessive in quantity It is this which is responsible for the clinical manifestations of thyrotoxicosis with the important exception of exophthalmos

The functional disturbance responsible for exophthalmos remains obscure In the guinea pig protrusion of the eyes follows the injection of T S H but it is by no means certain that this animal work gives rise to the same type of exophthalmos as is seen in the human An excess of T S H has been demonstrated in myxoedema but not in thyrotoxicosis yet exophthalmos is not seen in association with myxoedema and is seldom a pronounced feature of the severe generalized form of thyrotoxicosis It may be that the pituitary elaborates two types of thyrotrophic hormone one stimulating the thyroid and the other acting specifically on the orbital contents At present it is wise to accept the fact that exophthalmos is related to T S H but not directly to thyroid function, and to conclude that the protrusion of the eyes may be due to some disturbance of the pituitary-thyroid axis

SYMPTOMS AND SIGNS

The clinical picture of thyrotoxicosis is dependent on the degree of pituitary-thyroid activity and the response of the body to the hormonal stimulus No age group is exempt from the disease but it is most common in the third and fourth decade At all ages women are affected more often than men in a ratio of about four to one In the younger patients the presenting symptoms are nervousness fatigue loss of weight feeling of heat palpitations staring eyes and a swelling in the neck In older patients the constitutional disturbance may be minimal and the disease often presents as a cardiac disturbance or in the ocular form known as exophthalmic ophthalmoplegia

The natural history is prolonged often over years the condition varies in severity but the general course is downhill Occasionally a complete spontaneous remission occurs often related to a change in emotional en-

vironment. On the other hand a few patients have a continually active disease without apparent progression. In one patient the disease may be no more than an inconvenience in another so severe as to endanger life

The following analysis of clinical manifestations is based on the physiology of the disease

(1) *The Goitre*

If the thyroid enlargement appears simultaneously with functional overactivity the whole of the gland is involved presenting a uniform symmetrical swelling of smooth outline and rubbery firm consistency The increased blood flow is noticeable on auscultation when a hum with systolic accentuation will be heard For reasons poetic rather than scientific the noise has been called bruit du diable

The association of hyperthyroidism developing with enlargement of a previously normal thyroid is sometimes termed primary thyrotoxicosis in distinction to secondary thyrotoxicosis arising in a long standing goitre In the latter variety the thyroid is nodular or lobulated often asymmetrical in its enlargement and of a greater size than is common in the primary type of the disease It may be virtually impossible on palpation to determine whether the gland is lobulated or contains a discrete adenoma Luckily the point is of little practical importance

The goitre rarely causes a feeling of fullness of the neck Some patients complain of difficulty in swallowing which is not due to an organic lesion but akin to globus hystericus However retrosternal extension of the thyroid may cause mediastinal obstruction

(2) *Calorigenic Effects*

Thyroid hormone is a potent stimulator of the metabolic rate so weight loss is characteristic of the disease The degree of wasting will depend on the appetite and the increase in metabolic rate In some weight loss with disappearance of subcutaneous fat is a predominant symptom but in others the appetite is so increased that weight loss is minimal or absent It is a unique characteristic of thyrotoxicosis and diabetes mellitus that weight loss occurs with a good or even increased appetite

The heat production from the excessive metabolic rate is appreciated by the patient as a sensation of body warmth at all times with a marked intolerance for hot weather Heat is lost through the skin which is hot to the touch flushed and sweaty Marked vasodilation is present Generalized itching of the skin can occur in in the absence of any rash Despite its warmth and moistness the skin remains remarkably fine and silky in texture

(3) *Nervous System*

If the patient has an unstable personality nervous symptoms are likely to dominate the picture A short temper irritability and exaggerated emotional response make life unpleasant for patient and relatives alike Any psychiatric symptoms already present become worse with thyrotoxicosis Latent psychotics may become seriously ill from the mental point of view only to recover when the thyroid has been treated A confusion of neurotic symptoms often obscures the diagnosis of thyrotoxicosis and complicates the results of treatment

The inability to relax mentally is matched by a driving physical restlessness I feel like a dynamo is an aptly expressive phrase The constant movement of the patient so reminiscent of a bird on a bough makes the thyrotoxic demeanour a striking feature of the clinical interview

In marked contrast is a constant fatigue This may be accompanied by muscular weakness but loss of motor power is minimal and the characteristic finding is hypotonia with exaggerated tendon reflexes A fine tremor of the hands completes the picture so different from the coarse irregular trembling found in anxiety states

In rare cases the neuromuscular system is affected by myasthenia gravis (responsive to prostigmin) or by a chronic myopathy involving the muscles of the trunk and limbs which are weak and symmetrically wasted Such cases are often associated with the exophthalmic type of thyrotoxicosis

(4) *Ocular Signs*

The classically protuberant eyes of the thyrotoxic are due to a number of mechanisms which may be grouped as follows

(a) *Related to lid retraction*

Wide palpebral fissure
Staring expression
Lid lag

These signs may be related closely to an excess of thyroid hormone Cervical sympathetic overactivity plays some part in the causation Lid lag is so called because as the patient looks downwards the upper lid does not follow the movement of the eyeball Transient lid lag may occur in anxious people but as a constant phenomenon it is a helpful sign of thyrotoxicosis which disappears as the disease responds to treatment

(b) *Swelling of orbital contents* The eye is pushed forward by oedema and fat deposition in the orbit The fat may herniate around the eyeball

to produce a swelling of both upper and lower lids The resulting exophthalmos is often unilateral at the onset Diplopia results if the binocular axis is seriously disturbed

(c) *Swelling of conjunctiva* Visible oedema (chemosis) of the conjunctiva is due in part to exophthalmos and in part to superadded infection or trauma Failure of the eyelids to close over the exophthalmic eye renders it extremely susceptible to damage and it is in constant danger of destruction from corneal ulceration and pan-ophthalmitis Some protection is given by a constant stream of tears which is most uncomfortable for the patient

(d) *Weakness of extrinsic ocular muscles* The muscles are oedematous and infiltrated with fat and small round cells The weakness is most evident in the plane of movement rather than in the individual muscle Limitation of upward movement is the first and most severe restriction followed by failure of lateral movement. Diplopia is common The degree of exophthalmos is not directly related to the severity of the ophthalmoplegia

OPHTHALMIC TYPE OF THYROTOXICOSIS

The combination of exophthalmos and limited eye movements is not usual in the classical form of thyrotoxicosis Indeed it forms such a definite syndrome that some authorities separate the condition from thyrotoxicosis and term it exophthalmic ophthalmoplegia General evidence of thyrotoxicosis is minimal or absent but an episode of thyrotoxicosis is a common antecedent In particular the condition commonly follows successful treatment of generalized thyrotoxicosis

Thyroidectomy or the administration of goitrogenic agents may be followed by the most severe progressive protrusion of the eyes which deserves the title of malignant exophthalmos A sudden fall in thyroid function is likely to precipitate the condition and it occurs less commonly when antithyroid treatment produces a slow diminution in thyroxine secretion Radio-iodine therapy or carefully graded doses of antithyroid drugs appear to be less likely to produce exophthalmos than thyroidectomy or large intermittent doses of antithyroid agents Curiously enough the condition is most common in middle-age and affects both sexes equally in contrast to the incidence of classical thyrotoxicosis

(5) *Cardiovascular Effects*

Thyroid hormone has a direct excitatory effect on the heart as distinct from the indirect action of raising the cardiac output by virtue of an

increased metabolic rate In young patients a sinus tachycardia is the rule the pulse rate remaining elevated during sleep The excitability of the patient will enhance the tachycardia during waking hours The cardiac impulse is diffuse and forceful and a blowing systolic murmur is heard widely over the praecordium The patient frequently complains of palpitations especially after exertion Marked peripheral vasodilation is a feature of the condition and the fall in peripheral resistance increases the pulse pressure so that the pulse is either bounding or collapsing in character

In older subjects the cardiovascular system cannot withstand the extra stimulus of thyroid hormone Consequently relatively minor increases in thyroid function affect the heart with a minimum of constitutional disturbance Thyrocardiac disease does not arise solely from hyperthyroidism but is largely determined by the degree to which the heart is affected by degenerative disease The characteristic feature of these cases is auricular fibrillation at first paroxysmal and later permanent The rate of fibrillation is rapid and its response to digitalis unsatisfactory *Heart failure* may result but is very rare in the absence of fibrillation The presenting symptoms are palpitations and breathlessness the most obvious clinical signs are fibrillation and increased peripheral circulation Indeed any patient with auricular fibrillation in the absence of rheumatic carditis should be considered as a possible case of thyrotoxicosis particularly if the response to digitalis is poor

It must be noted that swelling of the ankles is a frequent early sign of thyrotoxicosis in the absence of heart failure It appears to be due to local circulatory changes in the same manner as the oedema of ankles so frequently experienced by healthy women in hot weather

(6) *Other Manifestations*

Thyrotoxic Crisis A dramatic and potentially fatal exacerbation of the disease may be precipitated by infection or thyroidectomy Adequate pre-operative therapy has virtually eliminated crisis after operation But on occasion incorrect preparation or a delay in operation until the patient s *disease has escaped from the influence of iodide therapy* or extremely hot weather at the time of operation will lead to this severe complication

The onset of crisis is abrupt Hyperpyrexia delirium and extreme tachycardia accompany profound collapse and hypotension The reason for this sudden breakdown in body resistance is obscure It may be that temporary adrenal insufficiency plays a part

Intestinal Some increase in the frequency of bowel action is a common event The symptom is often missed as the patient s bowel habit may have become regular in contrast to previous constipation. Occasionally frank diarrhoea is a presenting symptom The motion is watery but contains no blood or mucus Small intestinal hurry appears to be the cause

Menstrual Cycle Alterations in menstrual function are common varying from menorrhagia to amenorrhoea Such alterations are of no diagnostic significance but may alarm the patient

Osteoporosis Occasionally severe osteoporosis particularly affecting the spine afflicts the elderly thyrotoxic The exact mechanism of this obscure complication is unknown, but factors other than an excess of thyroid hormone are likely to be involved The results of adequate antithyroid therapy are not wholly satisfactory in the alleviation of the bone disease

Pre-tibial Myxoedema In this curious condition areas of mucinous infiltration give rise to a symmetrical indurated swelling on the front of both shins just above the ankle The skin may appear puckered like pigskin or reddened suggesting inflammation It occurs under the same circumstances as exophthalmic ophthalmoplegia and is found in association with it This localized myxoedema is not an indication of hypothyroidism but rather of the later stages of recurring thyrotoxicosis

Other Metabolic Effects Thyroxine increases the speed of absorption of sugar and has a mildly antagonistic effect to insulin Glycosuria may result from the ingestion of sugar because of rapid absorption with a transient rise in blood-sugar Latent diabetes mellitus may become obvious if thyrotoxicosis occurs or established diabetes made worse by hyperthyroidism There is no indication of a direct association between the incidence of diabetes and thyrotoxicosis

Impairment of liver function has been alleged as a complication of thyrotoxicosis There is no convincing evidence for this but in very rare instances hepatosplenomegaly is found in the disease and disappears when the thyroid is treated

DIAGNOSIS

Nothing is more obvious than frank thyrotoxicosis The less blatant forms of the condition are usually discernible by routine clinical methods but in some cases aids to diagnosis are of value The most common difficulty is the differentiation of neurotic states from thyrotoxicosis It

must be realized that the two conditions are not mutually exclusive and often co-exist The other problem is the identification of thyrotoxicosis as the cause of auricular fibrillation. Diagnosis in these instances can be more difficult in the presence of a goitre which may be non-toxic but at all times clinical acumen is more valuable than biochemical tests

Although the most common error is to confuse an emotional upset with thyrotoxicosis there may be a failure to recognize thyroid hyperfunction because a rare form of presentation dominates the picture Loss of weight without obvious physical abnormalities unilateral exophthalmos generalized itching of the skin or diarrhoea may be due to an excess of thyroid hormone and unaccompanied by obvious confirmatory signs Lastly thyrotoxicosis factitia must be mentioned because of its physiological interest Very occasionally patients who have taken thyroid extract for slimming become addicted to the substance When taken in sufficient quantities thyroid extract causes an increased basal metabolic rate tachycardia sweating anxiety and loss of weight Lid lag but no exophthalmos may be present. Moreover the thyroid gland is not palpable and radio-iodine uptake is very low as seen in hypothyroidism This unusual sequence of events suggest the self administration of thyroid extract which the patient will not admit unless questioned with considerable discretion

Aids to diagnosis provide data on thyroid function (radio-iodine techniques estimation of protein bound iodine) or on the body s response to thyroid activity (basal metabolic rate serum cholesterol creatine excretion) Each test has its own technical and physiological snags and none of them provide a diagnosis The value and limitations of each technique is described in the Appendix Determination of the basal metabolic rate has been for years the most important test of body response to thyroid activity Repeated determinations are essential but even under the most carefully regulated conditions anxiety or heart failure can increase the metabolic rate and malnutrition decrease it Despite these objections the test remains useful as a method of gaining information rather than indicating the diagnosis

Radio-active iodine in minute amounts has provided a useful and safe tool for measuring thyroid function Once again the information obtained is very valuable but not necessarily diagnostic However it does give a clear picture of the state of thyroid function and is the most useful aid to diagnosis at present available Chemical estimation of protein bound iodine gives an indication of the amount of circulating hormone but the technique has such difficulties that it is not reliable as a routine measure

Other indices of the effect of thyroid hormone are not of great diagnostic value Serum cholesterol is sometimes low in thyrotoxicosis but the change is inconstant At best a high serum cholesterol would militate against a diagnosis of thyrotoxicosis Similarly creatinuria occurs when muscle wasting is present but at that stage clinical diagnosis is obvious

Consideration of the physiology of thyrotoxicosis makes it obvious that all tests of thyroid function or hormone effect are incapable of giving a clear cut answer to the diagnosis For the disease is quantitatively not qualitatively different from normal thyroid function Thus in the development of the condition the thyroid will pass through all phases of activity from normal to high normal and on to frank hyperfunction Patients may be seen in the state of transition so that all available evidence is equivocal Under these conditions the finest diagnostic test is masterly inactivity for a few weeks and then clinical re-appraisal

TREATMENT

The condition fully justifies the motto treat the patient not the disease Before any decision is taken as to specific antithyroid therapy the patient s mental and environmental state must be assessed Adjustment of these factors is essential Sympathy and understanding are more important than sedation, although the judicious use of barbiturates is recommended

Methods of reducing the output of thyroid hormone are crude in theory but effective in practice The choice lies between removing a large portion of the overactive gland diminishing the amount of active tissue by radiation, or inhibiting the synthesis of hormone by drugs Each patient must be considered as an individual and the decision on the type of treatment based on the one most suitable for that particular person

(1) ANTITHYROID AGENTS

(a) *Iodine*

Iodine has a specific effect on thyrotoxicosis but no obvious effect when thyroid function is normal Given in amounts which are considerably above those required for hormone synthesis iodine has a very rapid effect on the disease the metabolic rate falls as quickly as after thyroidectomy (without pre-operative iodine) The symptoms and signs regress rapidly and the goitre becomes smaller and less vascular Colloid material re-accumulates in the vesicles and the lining epithelium diminishes in height If iodine is administered to the normal person there will be no drop in the metabolic rate Indeed the specific effect of iodine on the

raised metabolic rate of thyrotoxicosis and its lack of effect on metabolism in other conditions has been used as a diagnostic test

Although the immediate effect of iodine is dramatic it has no influence on the long term development of thyrotoxicosis and the disease escapes from its influence in a short while The maximum clinical effect of iodine is observed after two to three weeks administration After that time the signs and symptoms slowly reappear and are uninfluenced by further iodine medication The mechanism underlying this curious type of therapeutic response is obscure but it is probable that iodine temporarily inhibits the action of T S H on the thyroid

Iodine medication is effective by mouth at a minimum dose of 6 mg daily No further benefit is obtained by increasing the dose Iodides of all kinds are equally effective but Lugol s solution (iodine 5 parts potassium iodide 10 parts water to 100 parts) is the usual preparation A dose of 5 minims once to three times a day is adequate therapy

It is obvious that iodine is not a definitive treatment as it does not influence the natural history of thyrotoxicosis However its short term effect in diminishing the clinical severity of the disease and the vascularity of the goitre makes it an ideal pre-operative treatment It should never be used until the diagnosis is established and arrangements for operation made If the operation is delayed the patient may have escaped from the effects of iodine with the result that thyroidectomy is followed by a thyrotoxic crisis Long term iodine therapy should never be considered and it is wise to reserve iodine for pre-operative use alone

(b) *Thiouracil and its Derivatives*

These drugs inhibit the synthesis of thyroid hormone from the iodide trapped in the gland As the degree of inhibition can be controlled by varying the dose the output of thyroid hormone can be reduced to and maintained at a normal level Excessive dosage will produce temporary hypothyroidism As the level of circulating hormone diminishes the pituitary output of T S H increases causing further enlargement of the goitre with increased vascularity Exophthalmos may then increase sometimes to an alarming degree probably stimulated by the pituitary activity

Drugs of this group in common use are methyl and propyl thiouracil and the related compounds methimazole (mercazole) and carbimazole (neo-mercazole) These compounds particularly carbimazole have been found to have a full therapeutic effect with the minimum degree of toxicity The drugs are effective by mouth but excretion is rather rapid In

order to maintain a constant inhibiting effect on the thyroid repeated doses carefully spaced over 24 hours are necessary Irregular and excessive dosage is far more likely to produce large goitres and exophthalmos

Toxic effects include skin rashes pyrexia and arthralgia but the most important one is agranulocytosis The modern drugs rarely produce this dangerous complication, but it may still occur because of individual sensitivity At one time repeated white cell counts were performed on all patients receiving these drugs in an attempt to detect the early stages of agranulocytosis However its dramatic onset defies such routine testing which may succeed in giving false confidence to the physician and unnecessary worry to the patient. It is preferable to ask the patient to report any infection particularly of the throat

Thiouracil derivatives can be used either as a pre-operative measure or as long term treatment In a pre-operative role the drugs ensure that the surgeon will operate on a non-toxic gland, and the patient can continue the treatment until such time as it is convenient to operate Methyl or propyl thiouracil 50 mg 6 or 8 hourly or carbimazole 10 mg 8 hourly are adequate routines for initial dosage However the goitre may become more vascular and difficult to dissect if this is the only treatment Therefore iodine must be given for two to three weeks immediately prior to operation During this time the dose of the thiouracil drug may be reduced Such a medical preparation for operation requires considerable judgment as to the duration and dosage for each patient. On no account should iodine be given prior to starting the thiouracil as the effectiveness of the latter is seriously impaired Consequently it is extremely unwise to give a trial course of iodine to a patient on the idea that if the disease is not fully controlled then thiouracil derivatives can be given.

The case for long term drug treatment has been closely examined in the last twelve years Toxicity of the drugs is not a major concern at this moment There is no doubt that the patient can be maintained in an excellent state of health by such treatment. After initial control the dose can be dropped to about 25 per cent of that originally employed, and the drugs given twice daily To prevent frequent adjustment of the dose for every alteration of thyroid status a mixture of thyroxine and methyl thiouracil has been employed (*methyl thiouracil 50 mg to 0 1 mg l thyroxine*) This allows inhibition of the thyroid without an increased output of T S H or the occurrence of myxoedema Such a combination is very useful in practice

The immediate disadvantages to long term therapy are the persistence of the goitre and the necessity for daily tablet taking Both these points

are not fundamental objections but do become a great source of worry to some patients The prime objection to long term treatment is the high relapse rate when the course is eventually stopped Even after continuous treatment for a minium of a year about 50 per cent of cases will develop the disease again in the ensuing five years This failure to establish a cure is a serious drawback to the method and a further course is not always as effective as the first in controlling the disease However there is a group of patients who do not relapse presumably because their disease was of a naturally short duration Unfortunately it is very difficult to define this group prior to treatment Long term therapy is particularly useful for those who refuse operation or for whom radio-iodine therapy is unsuitable or when adequate surgery is not available and admission to hospital impractical

(2) SURGERY SUBTOTAL THYROIDECTOMY

Provided that adequate pre-operative treatment has been given subtotal thyroidectomy remains the treatment of choice for the majority of patients In skilled hands the operative mortality is under 0 5 per cent with a correspondingly low morbidity The incidence of recurrent thyrotoxicosis or myxoedema after operation is low but both conditions do occur However there is a very good chance of effecting a permanent cure The dangers of thyroidectomy include local haematoma formation damage to the recurrent laryngeal nerve and hypoparathyroidism The *latter is usually transitory but occasionally the parathyroids are removed completely* leading to permanent dysfunction Post-operative thyrotoxic crisis does not arise unless there has been inadequate preparation for operation Increasing exophthalmos may follow surgery but can occur after any type of antithyroid treatment

In assessing the suitability of the patient for surgery two major factors must be considered Firstly the quality of the surgery including the anaesthetic and nursing care must be of the highest order In the hands of the inexperienced surgeon the mortality of thyroidectomy is considerable If surgical facilities are poor long term medical treatment is preferable The second consideration regards the special features of the patient s disease A goitre especially with retrosternal extension that causes pressure symptoms must be removed Thyrotoxicosis arising in a long standing goitre is another indication for surgery On the other hand previous thyroidectomy makes further operation more difficult and to be avoided if possible Auricular fibrillation with heart failure increases the

operative risk and initial medical treatment must prove successful before surgery is considered Active exophthalmos is also an ominous sign indicating the possibility of malignant exophthalmos after operation Whenever exophthalmos is present to any degree immediate post-operative treatment with thyroxine or thyroid extract (gr 2-3 daily) is indicated and should be continued for at least two months

(3) RADIATION THERAPY RADIO-ACTIVE IODINE

Many years ago radiation therapy by means of a radium collar or deep X-ray was a popular method of treating thyrotoxicosis But the inconstancy of clinical response and the severity of skin reactions led to the abandonment of these techniques Interest was renewed when radio-active iodine became available The selective concentration of iodine by the thyroid provided a natural mechanism by which harmful total body and skin radiation could be avoided and at the same time ensured that the thyroid cells would receive adequate radiation from within The more overactive the individual cell the greater its avidity for iodine so that automatically it would attract to itself a larger amount of radiation than the less abnormal cell The isotope with an atomic weight of 131 (I^{131}) which has a half-life of eight days is the one in common use Its administration by mouth is not attended by any immediate risk of constitutional disturbance However the convenience of this treatment is balanced by a number of disadvantages The immediate problem is calculation of the correct dose At the present moment dosage determined by an estimate of thyroid weight and the uptake of a tracer dose of radio-iodine is not sufficiently accurate to ensure complete control of thyrotoxicosis in every case A second dose may be necessary or on the other hand permanent hypothyroidism may result from one dose The chances of a rapid cure are less with radio iodine than with subtotal thyroidectomy but isotope therapy is still in its early days and the calculation of dosage will become far more accurate A further limitation is the slow clinical response to radiation but this may be overcome by preliminary treatment with anti-thyroid drugs discontinued shortly before administration of radio-iodine The last problem concerns the possibility of radiation carcinogenesis affecting the thyroid many years after treatment This is a theoretical possibility rather than a probability

Despite these difficulties radio-iodine plays a very definite role in the treatment of patients over 45 years old (The age limit is a reasonable convention to offset the possibility of late tumour formation) In cases

where the risk of surgery is high or in those who refuse operation and are ensitive to anti-thyroid agents it is the treatment of choice Patients with thyrotoxicosis recurring after thyroidectomy thyrocardiac disease or progressive exophthalmos should be considered for radio-iodine therapy in preference to other methods But the presence of a large or adenomatous goitre is an indication for surgery not radiation

Enough has been said about treatment to indicate the need for individual assessment and the considerable prospect of success if a rigid all embracing routine is avoided But certain aspects of thyrotoxicosis still lack an adequate therapy For instance thyrotoxic crisis which should of course be prevented is not readily responsive to any of the known antithyroid measures Cooling the patient with a fan and ice-packs together with the administration of iodides and sedatives are essential steps in treatment Recently cortisone given orally (50 mg every 6 hours) or intramuscularly (100 mg twice daily) has proved to be effective and should be used in every case

The real problem of therapy is found in exophthalmic ophthalmoplegia All methods have their exponents but all are disappointing Attempts at suppressing pituitary activity by giving thyroid extract oestrogens or deep X-ray to the gland are successful in some cases but inconstant in their effect More recently deep X-ray to the orbits has achieved a limited reputation In severe cases when blindness threatens surgical closure of the eyelids saves the eye from destructive infection. This is palliative only and the eyes can be returned to a normal position only by the major operation of orbital decompression as devised by Naffziger Despite its hazards this operation can be brilliantly successful and should be considered in all cases of serious progressive exophthalmos The operation may also be indicated in some instances of non-progressive but persistent severe exophthalmos

Hypothyroidism

The classical description of myxoedema and cretinism marked an enormous advance in the study of clinical endocrinology but told nothing of the various types of hypothyroidism and gave the impression that the clinical effects of thyroid deficiency cannot be diagnosed in the absence of the grossest physical signs The varieties of hypothyroidism are tabulated below the disease is described in children and then in adults because the appearances of the disturbance are dependent on the age of the patient

CLASSIFICATION OF HYPOTHYROIDISM

1 Primary Thyroid Failure (a) Spontaneous	(1) Infants	Congenital Hypothyroidism Endemic goitrous cretin Sporadic cretin ( ) Goitrous (b) Non-goitrous
	(2) Children	Juvenile myxoedema
	(3) Adults	Primary myxoedema Chronic thyroiditis
(b) Induced	After thyroidectomy After radiation With antithyroid drugs	
2 Secondary Thyroid Failure	Hypopituitarism with failure of T S H secretion	

Congenital Hypothyroidism Cretinism

Aetiology

A cretin is a child born with impaired or absent thyroid function Endemic cretinism now fast disappearing occurs in areas of severe iodine deficiency the goitrous mother giving birth to a goitrous child whose thyroid is permanently functionless Iodine medication has no effect on the child s thyroid Sporadic cretinism occurs in this country and others where there is no area of gross iodine deficiency Of course there is no reason to suppose that similar cases do not occur in endemic areas which brings up the argument that little difference exists between endemic and sporadic types However the lack of iodine during embryonic life is the cause of true endemic cretinism while congenital defects of anatomy or thyroidal enzyme systems lead to cretinism of the sporadic type The congenital anatomic abnormality is actual absence of the thyroid termed athyrotic hypothyroidism But interest has been aroused recently in cretins with a palpable thyroid who have an inborn error of metabolism which prevents the normal synthesis of hormone In some the thyroid is able to trap iodine but fails to convert it to organic compounds In others incomplete organic binding takes place but the normal hormone is not produced It is apparent that there is a congenital absence of one or more enzyme systems and as in other genetically determined metabolic errors there is a strong familial incidence

CLINICAL PICTURE

The effects of a depressed metabolic rate are the dominant features of adult hypothyroidism but in children the emphasis is on the failure of growth and maturation In the early days of its life the baby shows little or no evidence of hypothyroidism because its body is still influenced by

maternal thyroid hormone The appearance of symptoms and signs is insidious and this accounts for delay in diagnosis

The mother notices that her baby is a lazy feeder and fails to gain weight The associated lethargy may be interpreted as evidence of good behaviour A little later dryness of the skin and constipation become troublesome After that failure of mental development gradually becomes apparent from the baby s lack of interest in its surroundings Physical development in terms of teething sitting up or crawling is grossly delayed *In brief the baby fails to thrive*

The appearance of full blown cretinism is diagnostic The child is undersized for its age with short sparse hair and dry thickened yellowy tinted skin Puffiness of the eyelids thickened lips large protruding tongue depressed bridge of the nose snuffling breathing and a hoarse cry make the face reminiscent of a pig The limbs are thin and cold in contrast to the distended abdomen usually crowned with an umbilical hernia On palpation a greatly dilated colon full of hard faeces may be found Further evidence of delayed growth is evident from the late appearance of the teeth and from the open fontanelles of the skull (Normally the posterior fontanelle closes at four months and the anterior by eighteen months of age)

If the diagnosis of cretinism is delayed until the full clinical picture is immediately evident permanent mental damage will have occurred It is of the utmost importance to strive for early diagnosis to preserve intelligence by prompt treatment By the age of two the cretin will have become mentally deficient to the point of idiocy and treatment will not restore intelligence Consequently the possibility of hypothyroidism must be considered in all infants who fail to thrive (in the absence of obvious dietetic or gastro-intestinal disturbances) Puffiness round the eyes a pale dry rather thickened skin late dentition constipation and an umbilical hernia *are all early signs of thyroid deficiency* The presence of a goitre is obviously significant and cretinism in other members of the family a valuable pointer to a correct diagnosis

DIAGNOSIS

In rare instances transient hypothyroidism with a goitre occurs in babies born to mothers treated with large doses of thiouracil throughout pregnancy The evanescent nature of the disturbance and the mother s history make the diagnosis clear The main problem of diagnosis lies in the separation of various types of mental defect from hypothyroidism In particular Mongolian idiocy may have a superficial resemblance to cretinism be-

cause both conditions are associated with a depressed bridge of nose and a protuberant tongue But the Mongol derives its name from the slanting set of the eyes and the texture of its skin is finer than that of a cretin. The short curved little finger excessive flexibility of the joints and the frequent association of congenital abnormalities are features distinctive of the Mongol. Although there is a gross defect of intelligence in both conditions the cretin is lethargic and slow in comparison with the active often cheerful Mongol.

Estimations of the basal metabolic rate are not possible in the infant, but it is both safe and practical to determine the uptake of radio-iodine by the thyroid The complete absence of radio-iodine concentration in the neck region of the athyrotic cretin gives positive proof of hypothyroidism. On the other hand the thyroid of the goitrous cretin may be avid for iodine so that uptake studies may fail to help in the initial diagnosis Special techniques are required to determine the nature of the thyroid failure and radio-iodine plays an important part in this field

A high serum cholesterol and depression of the S-T segment of the electrocardiogram are useful confirmatory signs of hypothyroidism in the infant as well as the adult Finally X-rays of the epiphyses (i e of wrist and hand) are of great importance because hypothyroidism not only delays the appearance of centres of ossification but also causes a characteristic epiphyseal dysgenesis in which the homogeneous shadow of normal calcification in a centre of ossification is replaced by irregular patchy calcification with a fluffy indistinct margin. This appearance is diagnostic of hypothyroidism but is not present at all times Serial X-rays increase the probability of its detection.

If after proper investigation the diagnosis remains in doubt it is legitimate to give a therapeutic trial of thyroid extract Continuous treatment for at least two months and frequent examination is necessary before any conclusion can be reached as to the efficacy of thyroid extract. A definite response in terms of symptoms and signs indicates that hypothyroidism was present prior to therapy

TREATMENT

The diagnosis of cretinism must be followed by thyroid therapy for the rest of the patient s life As the child improves it is only natural for the mother to stop treatment This would be a major tragedy so that the significance of daily treatment must be stressed by every possible means

The initial dose of thyroid extract should be $\frac{1}{8}$ grain daily rising week by week to $\frac{1}{2}$ grain daily This will usually suffice as a maintenance dose

maternal thyroid hormone The appearance of symptoms and signs is insidious and this accounts for delay in diagnosis

The mother notices that her baby is a lazy feeder and fails to gain weight The associated lethargy may be interpreted as evidence of good behaviour A little later dryness of the skin and constipation become troublesome After that failure of mental development gradually becomes apparent from the baby s lack of interest in its surroundings Physical development in terms of teething sitting up or crawling is grossly delayed In brief the baby fails to thrive

The appearance of full blown cretinism is diagnostic The child is undersized for its age with short sparse hair and dry thickened yellowy tinted skin Puffiness of the eyelids thickened lips large protruding tongue depressed bridge of the nose snuffling breathing and a hoarse cry make the face reminiscent of a pig The limbs are thin and cold in contrast to the distended abdomen usually crowned with an umbilical hernia On palpation a greatly dilated colon full of hard faeces may be found Further evidence of delayed growth is evident from the late appearance of the teeth and from the open fontanelles of the skull (Normally the po terior fontanelle closes at four months and the anterior by eighteen months of age)

If the diagnosis of cretinism is delayed until the full clinical picture is immediately evident permanent mental damage will have occurred It is of the utmost importance to strive for early diagnosis to preserve intelligence by prompt treatment By the age of two the cretin will have become mentally deficient to the point of idiocy and treatment will not restore intelligence Consequently the possibility of hypothroidism must be considered in all infants who fail to thrive (in the absence of obvious dietetic or gastro-intestinal disturbances) Puffiness round the eyes a pale dry rather thickened skin late dentition constipation and an umbilical hernia are all early signs of thyroid deficiency The presence of a goitre is obviously significant and cretinism in other members of the family a valuable pointer to a correct diagnosis

DIAGNOSIS

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to the age of two years As the child grows older the dose must be increased reaching about 2 grains at the age of four years The adult dose is in the range of 4 grains daily A common cause of ineffective treatment is the failure to alter the dose with increasing age

As the correction of hypothyroidism is a matter of urgency in terms of mental health *initial therapy with tri-iodothyronine (0 01 mg once or twice daily)* has a definite advantage over thyroid extract or thyroxine which requires at least two weeks to achieve a significant result However the short term action of a dose of tri-iodothyronine makes it less satisfactory for maintenance treatment

Given early and continuous therapy the prognosis of cretinism is good The degree of mental defect is dependent upon the primary defect and the age at which treatment was started Although therapy prevents further decline in intelligence it does not cause any marked improvement in the mental state

Juvenile Hypothyroidism

Aetiology

In contrast to cretinism this is an acquired disease the cause of which is as obscure as in the adult Histological changes in the thyroid are those of atrophy and fibrosis

CLINICAL ASPECTS

The disease may arise at any time during childhood The early cases may be confused with true cretinism but gross mental defect is not a feature of acquired hypothyroidism The onset is insidious the previously normal child gradually slowing up in growth physical activity and mental acuity The teacher notices the child gradually descending the order in class and refusing to play during the school breaks The child complains of fatigue excessive cold and the appetite diminishes The skin becomes dry and pale with some puffiness of face A moderate degree of obesity may be present The extremities are unduly cold and constipation is common Slowing up of maturation delays the onset of puberty and the disease may present as sexual infantilism

Skeletal growth is also retarded and the bone age as determined by X-ray will be below the chronological age Epiphyseal dysgenesis may occur and can be misdiagnosed as Perthes disease of the hips

DIAGNOSIS

The aids to diagnosis and the conditions which may be confused with this disease are similar to those for adult myxoedema with the addition

of the various forms of sexual infantilism which have to be distinguished from hypothyroidism

One particular problem remains which should be discussed in this context Very frequently children are brought to the physician with a history of long continued thyroid therapy following an initial diagnosis of hypothyroidism As the child is perfectly well the parents are anxious to know whether or not thyroid disease is still present Sometimes excellent recorded evidence for the correctness of the diagnosis is available Under these circumstances it is obviously necessary to maintain thyroid therapy However there may be no indication as to how the original diagnosis was made Physical examination will reveal no evidence of hypothyroidism in the presence of adequate substitution therapy and radio-iodine studies are useless because treatment will have arrested the production of hormone by a normal gland. The only method is to stop thyroid therapy for three to six weeks The appearances of clinical signs of hypothyroidism and a rising serum cholesterol will confirm the original diagnosis If after six weeks the child remains normal and radio-iodine uptake will give a valid result and a normal uptake indicates that hypothyroidism is not present On the rare occasions that a child of under three years presents with this problem it is wise to delay a decision for at least a year as withdrawal of thyroid therapy at this age may cause irreparable mental damage

Myxoedema Adult Hypothyroidism

Aetiology

The spontaneous cessation of thyroid activity in the adult is accompanied by fibrosis and atrophy of the gland Hypothyroidism may also occur in the course of chronic thyroiditis in which the gland is enlarged and shows gross infiltration with small round cells (Hashimoto s type of thyroiditis)

Surgical removal of the thyroid is followed by the rapid onset of hypothyroidism in contrast to the slow evolution of the spontaneous type In some cases an error of judgment results in too much thyroid tissue being removed but in others the gland removed at operation shows lymphadenoid changes similar to thyroiditis There is no clinical difference in the thyrotoxicosis of these patients but it has been found that the majority of patients who develop post-operative myxoedema have thyroids of this type

The increasing use of radio-iodine has led to the production of a number of cases of post radiation myxoedema In some transient hypothyroid-

ism occurs but disappears spontaneously within six months Similarly the thiouracil group of drugs will cause hypothyroidism if given in excess but cessation of therapy is followed by a return to normal thyroid function

The physician is well aware of the possibilities of hypothyroidism following the use of these antithyroid agents but there are allied substances whose therapeutic use is not connected with thyroid disease Para-amino-salicylic acid and thio-semi-carbazone both used in the treatment of tuberculosis are examples of this group Thiocyanate once used for hypertension proved a potent antithyroid agent its action differing from thiouracil in that it inhibits the uptake of iodide and not the synthesis of hormone More recently resorcinol a constituent of many ointments used for skin ailments has been found to cause hypothyroidism after absorption from varicose ulcers The introduction of cobalt for the treatment of certain anaemias has added another drug to the list of those capable of inducing hypothyroidism in association with an enlarging thyroid

Clinical Picture

Spontaneous hypothyroidism is mainly a disease of women under 10 per cent of cases being male It may arise at any age but is rare outside the range of 30–60 years The onset is extremely insidious so that at least a year may elapse from the first symptom to the final diagnosis

Symptoms

These are related to the decrease in metabolic rate Physical fatigue and mental torpor slowly envelop the patient The daily round becomes more onerous and takes longer to complete Memory and power of concentration become poor but intelligence and humour usually remain An intense feeling of cold is characteristic indeed a light hearted generalization that a fur coat at Ascot is pathognomonic has some truth but does not allow for the vagaries of the English summer Breathlessness on exertion or even anginal pain may be presenting symptoms Constipation is common and the appetite is often impaired Diffuse aches and pains in the limbs add to the patient s general misery Lastly the characteristic change in appearance may be noted by the patient and lead her to seek advice

Physical Signs

A mucinous infiltration of the skin gives rise to the term myxoedema and to the general appearance of the patient The complexion becomes

pale with a yellow tint and a patch of redness on the cheeks Peaches and cream may describe the colouration but is inappropriate to the rough texture of the thickened skin *Myxoedematous infiltration thickens the* eyelids which become very puffy in the morning the lips and the vocal cords The voice becomes hoarse and monotonous A dry skin with absence of sweating is found all over the body The patient is often aware of the thickening saying that her face feels stiff and her whole body bloated. The scalp hair becomes lustreless and thin. Body hair is reduced but never disappears *Absence of the outer third of the eyebrow has been* noted as common but is an unreliable sign because it is so frequently seen in normal people

Some gain in weight is common, partly depending on water retention but marked obesity is very rare as the appetite tends to diminish with the rate of metabolism Achlorhydria may be present The abdomen becomes distended because of *constipation* and *dilatation of the colon*

The patient moves in slow motion the manner of entering the consulting room suggests the correct diagnosis Some loss of motor power may be detected but the most obvious neurological abnormality is the sluggish reaction of the tendon reflexes Deafness is a further complication occasionally pure nerve deafness but mostly of a mixed type

Enlargement of the heart sometimes with *heart failure is a common* finding There is some debate as to whether the apparent cardiac enlargement is due to the involvement of the myocardium by the myxoedemic process or from a pericardial effusion Both events probably occur Certainly the size of the heart shadow on fluoroscopy diminishes after the administration of thyroid extract The pulse is regular and slow although *marked bradycardia is infrequent Coronary artery disease is common* probably in association with a raised serum cholesterol It is pertinent to remember that anginal pain in women is suggestive of myxoedema or diabetes mellitus Hypertension may complicate the picture but it is not typical of hypothyroidism. The electrocardiogram shows a low voltage record with depression of the S-T segment in all leads

A lowering of the *metabolic rate appears to affect the bone marrow as* anaemia is a constant finding often enhancing the tendency to water retention, so that pitting oedema of the ankles is present as well as the mucinous infiltration of the skin Normochromic hypochromic and hyperchromic anaemias have been described In some patients thyroid extract alone corrects the anaemia but in others iron is necessary as well A few respond to liver extract or Vitamin B 12 but this suggests a fortuitous association of pernicious anaemia and hypothyroidism.

Just as anaemia or cardiac disease may dominate the clinical picture so gross psychosis can be a presenting sign of thyroid failure The mental reaction in myxoedemic madness varying from depression to acute agitated mania is not specific

Myxoedema is a relatively benign disease incapacitating yet seldom directly fatal However a terminal phase of coma can occur in which the metabolic rate falls so low that heat production is insufficient to maintain the body temperature The whole body metabolism comes slowly to a stop The patient shows every appearance of gross myxoedema in a coma so deep as to suggest that death has already occurred Respiration is shallow and irregular and the pulse imperceptible the heart being just audible at twenty to thirty beats a minute The skin is as cold as that of a corpse and the rectal temperature may be as low as 90° F Recovery from this state is understandably rare

DIAGNOSIS

Primary hypothyroidism has to be distinguished from the secondary variety due to pituitary failure Indeed this may be difficult because long standing myxoedema results in impaired adrenal function (as judged by tests of function) and delay of sexual maturation in the young patient In both types of hypothroidism lethargy is a feature but gross muscular weakness and collapse after infection are characteristic of the secondary type as these symptoms are due to adrenal failure But the absence of any space-occupying lesion in the pituitary region or history of post-partum shock and no evidence of early and complete hypogonadism or hypoglycaemia point to primary thyroid disease The texture and colour of the skin differs in the two conditions The thickened rough yellow tinted skin of myxoedema contrasts with the soft smooth chalk-white though puffy skin of panhypopituitarism Body hair is rather scanty and scalp hair very thin in myxoedema compared to the almost complete absence of body hair with fine scalp hair of pituitary failure

Occasionally the facies in Addison s disease gives an impression of hypothyroidism because of rather puffy eyelids and thin eyebrows The association of this with a complaint of lethargy and sensitivity to cold may suggest the diagnosis but these symptoms are also common in chronic adrenal failure and the smooth pigmented skin indicates the correct diagnosis of Addison s disease It must be remembered that hypothyroidism occurs in a small number of cases of adrenal failure so that investigation of thyroid function is always worth while

Anaemia of all types may suggest hypothyroidism but it is more

common to diagnose persistent anaemia and fail to realize that it is due to thyroid insufficiency Type II nephritis in the nephrotic phase resembles myxoedema in that a pale puffy face and high serum cholesterol are common to both diseases As albuminuria is sometimes present in myxoedema the hypothyroid patient may be diagnosed incorrectly as suffering from nephritis Such difficulties are only present on cursory inspection a proper history and examination is sufficient to distinguish the two conditions

The diagnosis of myxoedema provides one of the few occasions in which the family photograph album can be put to practical use as a change in the facial appearance is so characteristic of the disease Comparison with earlier photographs of the patient can give reasonable evidence of such change and makes it possible to date this against the onset of symptoms

Special tests for hypothyroidism are similar to those for thyrotoxicosis The basal metabolic rate is of value although the patient s anxiety about the test may give a falsely high value On the other hand a B M R of 15 per cent or lower is very suggestive of hypothyroidism if the patient is well nourished Radio-iodine techniques are not so reliable as in thyrotoxicosis because iodine uptake and discharge may not be widely different from the lowest level of normal function If hypothyroidism is due to thyroiditis or induced by antithyroid agents radio-iodine will not be of diagnostic value although of great help in determining the mechanism of thyroid failure A carefully observed therapeutic trial of thyroid extract as suggested in the section on juvenile hypothyroidism is recommended when the diagnosis is not clarified by investigation

The serum cholesterol is raised in most cases of myxoedema but is also raised in many other conditions However serial cholesterol determinations act as a useful indication of the response to treatment Other relevant investigations include an electrocardiogram radiological determination of heart size and a full blood count

TREATMENT

The first successful therapy in endocrinology was the administration of a thyroid extract to a myxoedemic patient Thyroid extract of standardized potency remains the logical routine treatment today A pure hormone is available now in the form of l thyroxine and a further advance has been the preparation of tri-iodothyronine But these substances are no more efficient than thyroid extract (B P) All are fully effective on oral administration but tri-iodothyronine has a remarkable speed of action

which is short lived The clinical value of rapid return to normal metabolism is problematic and there is less danger in a slower response particularly if the heart is myxoedematous

As a rough comparison of potency thyroid extract gr ½ is equivalent to l-thyroxine *0 05 mg or tri-iodothyronine 0 01 mg* *Thyroid extract* has the same speed and duration of action as l-thyroxine but the latter has the academic advantage of being a pure substance Either is successful in treatment given in one oral dose daily Initial dosage depends on the severity of the disease severe myxoedema is responsive to a smaller dose than is required for the mild case Thyroid extract gr ½ or its equivalent as l-thyroxine is adequate as an initial daily dose for severe myxoedema while gr 1 or even gr 2 is a safe dose for the milder case The particular dose ought to be continued for at least two weeks before any change is contemplated as this time is required for the body to reach a maximum response Final maintenance dosage lies between 2 and 5 grains daily it is exceptional to find a patient who requires more than this An apparent need for massive thyroid therapy suggests that the thyroid extract is impotent the patient failing to take the tablets or an error in diagnosis has been made

The response to treatment is judged best on purely clinical grounds without recourse to serial determinations of metabolic rate for the patient usually reaches optimum health when metabolism is on the low side of normality

Thyroiditis

The acute forms probably infective in origin do not appear to have any aetiological relationship to chronic thyroiditis which is unlikely to be inflammatory in origin

Acute and Subacute Thyroiditis

The responsible organism is unknown but the occurrence of acute thyroiditis in association with specific fevers or local infections of the teeth or throat makes it probable that several agents may influence the thyroid Spontaneous resolution is the rule but suppuration can occur

The onset is sudden pyrexia and general malaise being associated with a tender swelling of the thyroid which makes swallowing or moving the neck very painful Examination reveals a diffuse firm tender swelling of the thyroid often involving only one side The overlying skin is hot and may be reddened

Diagnosis depends on identifying the inflammatory mass as the thyroid

by detecting its movement on swallowing Cellulitis of the neck mimics the symptoms and outward appearance of thyroiditis On the other hand haemorrhage into a pre-existing goitre gives a tender localized swelling of an enlarged thyroid without the constitutional disturbance

CHRONIC THYROIDITIS

Two distinct histological types are seen neither following upon acute thyroiditis Each type has its own distinctive natural history the aetiology of both is unknown and their mutual relationship uncertain

CHRONIC LYMPHADENOID THYROIDITIS (HASHIMOTO S TYPE)

A lymphoid infiltration invades the whole gland which is diffusely enlarged Small round cell infiltration is seen with lymph follicles and some giant cells Some fibrosis is present but is not marked The degree and uniformity of cellular infiltration and fibrosis can be variable Sometimes only part of the thyroid is involved by the condition.

This type of thyroiditis is usually found in middle age and affects women almost exclusively The presence of pressure symptoms and the goitre itself are the main complaints The goitre is smooth, symmetrical and of firm consistency The trachea may be displaced but is seldom constricted Although there may be symptoms suggestive of thyrotoxicosis in the earlier phase of the disease frank myxoedema invariably appears in the later stages The plasma proteins are often qualitatively abnormal

CHRONIC FIBROUS THYROIDITIS (RIEDEL S TYPE)

In this very rare condition the thyroid becomes enlarged stony hard and firmly adherent to the trachea However the goitre still moves on swallowing and is not adherent to the overlying skin. The gland is converted into a dense mass of fibrous tissue so hard that it is difficult to cut The process develops at a variable rate sometimes advancing rapidly in a few weeks at others taking many months to develop fully

Two out of three patients with Riedel s thyroiditis are women usually afflicted in middle age The patient complains of stridor and dysphagia with a constant feeling of pressure on the neck. The characteristics of the goitre are its stony hardness and close application to the trachea It is surprising that hypothyroidism is by no means a constant finding and is seldom severe in its manifestations

DIAGNOSIS

The goitre of thyroiditis is to be distinguished from carcinoma or

sarcoma of the thyroid and from a non-toxic goitre with adenomata The smooth contour of lymphoid thyroiditis and its association with hypothyroidism is unlike carcinoma or a non-toxic goitre However clinical distinction of thyroiditis from a neoplasm of the thyroid is often impossible so biopsy or even resection of the gland may be necessary for a final diagnosis

TREATMENT

Operative removal is required to cure pressure symptoms In the lymphoid type favourable response to deep X-ray therapy often makes an operation unnecessary provided the diagnosis is certain. It is important to keep these patients under observation to detect hypothyroidism in its early stages The administration of thyroid extract will not only relieve the symptoms of hypothyroidism but can be used in the earlier stages of the disease to decrease the size of the goitre

CHAPTER V

THE ADRENALS

ANATOMY

THE adrenal glands are two small flattened bodies lying behind the peritoneum immediately in front of and above each kidney The right adrenal is roughly triangular and the left crescentic in shape Each weighs from 3-4 grams and consists of an outer cortical portion rich in lipoids and an inner medulla consisting of chromaffin tissue The two portions are distinct in histology embryology and function. The medulla arises from the chromaffin cells which are the forerunners of the sympathetic ganglia and the cortex is derived from the coelomic epithelium

The adrenal cortex consists of a fine connective tissue network in which is embedded the glandular epithelium These cells are arranged in rounded groups below the capsule to form the zona glomerulosa with a deeper layer or zona fasciculata arranged radially An inner layer next to the medulla is the zona reticularis consisting of irregularly arranged columns of cells The medulla is extremely vascular and is composed of large chromaffin cells interspersed with venous sinusoids

PHYSIOLOGY

(1) *Medulla*

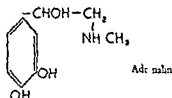
The adrenal medulla forms part of the sympathetic system which secretes adrenalin and nor-adrenalin This secretion is under nervous control Adrenalin is rapidly destroyed in the body so that its action is transitory Its effects are similar to those produced by stimulation of the sympathetic nervous system and it is therefore classed as a sympathomimetic substance As the action of adrenalin and the autonomic nervous system is so well described in textbooks of physiology and pharmacology no full account of adrenalin will be given here It is sufficient to add that nor-adrenalin is entirely vasoconstrictive in action having little effect on the heart in contrast to adrenalin This point is important in relation to functioning tumours of the medulla and the therapeutic use of nor-adrenalin infusions

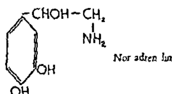
As the adrenal medulla is only part of the sympathetic ganglion system it is not surprising that its presence is not essential to life or health

(2) *Cortex*

The hormones elaborated by the adrenal cortex are all steroids being

synthesized from cholesterol The exact number of active hormones is still unknown as so many have been isolated from adrenal tissue The physiological activity of each hormone is shared to some degree by the others consequently it is impossible to ascribe the physiological effects of adrenal secretion to the separate action of each hormone A normal adrenocortical secretion is essential to health and the absence of these hormones is fatal



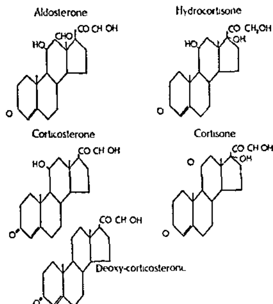


HORMONES OF ADRENAL MEDULLA

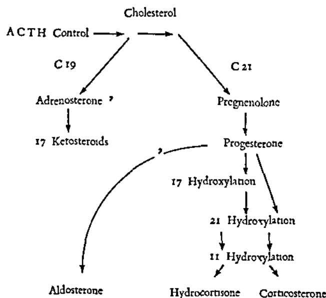
Chemistry of Adrenal Cortical Hormones The bald fact that thirty different steroids have been isolated from the adrenal cortex is merely confusing unless it is realized that many of these compounds are formed as steps in the biosynthesis of the adrenal secretion

The adrenal cortex is rich in cholesterol the base material from which adrenal steroids are formed The sequence of events and the formulae of the hormones are summarized in the accompanying diagrams and the important steps are as follows

(1) The side chain of cholesterol is split off giving rise to two series of hormone precursors one group containing 19 carbon atoms (C19 *steroids) and the other 21 carbon atoms (C21 steroids) This initial process* is controlled by A C T H There is little evidence to suggest that it regulates any other step in biosynthesis Hence the anterior pituitary controls the adrenocortical rate of secretion simply by regulating the amount of hormone precursors which are available to the adrenal enzyme systems that synthesize the hormones (with the probable exception of aldosterone)



ADRENAL STEROIDS



BIOSYNTHESIS OF ADRENAL STEROIDS

(2) C19 steroid precursors have not as yet been identified They give rise to the adrenal androgens as represented by adrenosterone and androsterone These hormones have a ketone group at the 17th carbon atom and provide the greater part of the adrenocortical contribution to urinary 17-ketosteroids

(3) The C21 steroid precursor has been identified as pregnenolone which is oxidized to progesterone The latter is the key substance in the synthesis of C21 steroid hormones Hydroxylation of the 21st and 11th carbon atom of progesterone forms corticosterone Hydroxylation of the 17th carbon atom of progesterone followed by hydroxylation of the 21st and 11th carbon atom forms hydrocortisone Aldosterone is also formed from progesterone but its pathway of synthesis is still unidentified

Hydrocortisone is the principal constituent of the adrenocortical secretion in man It has a weak effect on electrolytes but a powerful effect on carbohydrate metabolism and is therefore termed a glucocorticoid Cortisone is also a glucocorticoid and is present in small amounts in systemic blood probably being formed from hydrocortisone at some site other than the adrenal

Aldosterone is a weak glucocorticoid but immensely potent in its effect on electrolytes and is therefore termed a mineralocorticoid Corticosterone possesses about 1/200 of the mineralocorticoid potency of aldosterone but its serum concentration is about one hundred times greater Therefore in terms of normal physiology both hormones must be considered as effective mineralocorticoids

The adrenocortical secretion contains not only androgens but also small amounts of oestrogens and pregestational hormones The adrenal androgens are not so potent as testosterone (secreted by the testis) However adrenal oestrogens are similar in their chemistry and physiological effect to those secreted by the ovary The important role of progesterone in hormone synthesis makes it obvious that progestational substances can be extracted from the adrenal

Physiology of Adrenal Cortical Hormones

(1) Mineralocorticoids

The mineralocorticoid secretion of the adrenal maintains the normal balance of sodium and chloride within the body Adrenalectomy results in a loss of sodium and chloride from the body because of an increased urinary excretion of these ions Dehydration follows because the volume of water excreted is also increased One of the results of dehydration is a

lowering of plasma volume In consequence the serum concentrations of sodium and chloride appear to be normal until the urinary loss of salt has continued for some time When the serum levels of sodium and chloride do fall to subnormal values the urinary loss of these elements still continues The persistence of a high urinary sodium chloride concentration when the body is obviously dehydrated and salt deficient is typical of adrenocortical failure and in contrast to other forms of salt deficiency

While adrenalectomy increases the renal loss of sodium it decreases the urinary excretion of potassium At the same time potassium passes from the cells into the serum as a result of a falling serum sodium concentration. By these two mechanisms serum potassium reaches abnormally high concentrations

The administration of mineralocorticoids to the adrenalectomized subject will restore normal electrolyte balance These hormones act at the level of the renal tubule increasing the tubular reabsorption of sodium and chloride from the glomerular filtrate and decreasing the reabsorption of potassium. Thus sodium and chloride are conserved and excess potassium is lost For this reason the serum or urinary ratios of sodium to potassium are more valuable than the individual concentration of either element as a guide to adrenal failure or the action of mineralocorticoids

As a direct effect of mineralocorticoid control of sodium and potassium in the adrenalectomized subject the plasma volume returns to normal and dehydration disappears

The effect of overdosage with mineralocorticoids has been demonstrated with the synthetic hormone deoxycorticosterone (deoxycortone B P) Excessive storage of sodium results in oedema cardiac dilation and hypertension, which can lead to heart failure Coincident with sodium retention there is a loss of potassium excreted in the urine and a fall in serum potassium sometimes to dangerously low levels

(2) *Glucocorticoids*

The biological assay for these hormones is dependent on their ability to increase liver glycogen deposition. However the deposition of glycogen is accompanied by a rise in blood sugar as gluconeogenesis from protein is accelerated and the peripheral action of insulin is impaired Hence a tendency to hypoglycaemia and extreme sensitivity to insulin is found after adrenalectomy and is counteracted by the administration of glucocorticoids

Physiological speaking the action on carbohydrate metabolism is not so important as the protective action on the body subjected to injury

The underlying mechanism remains obscure but the administration of glucocorticoids to the adrenalectomized animal will prevent it succumbing to minor trauma

Another type of action concerns the promotion of normal water diuresis The adrenalectomized animal cannot secrete a water load even when mineralocorticoids are administered Normal renal excretion of water is restored by glucocorticoids Overdosage with glucocorticoids results in protein breakdown excessive gluconeogenesis and loss of potassium from breakdown of cells leading to a diminution in body protein and an increase of fat (storage of excess carbohydrate)

(3) *Androgens*

Adrenal androgens are less potent than those secreted by the testis but in the female play a large part in the growth of axillary and pubic hair Apart from sex effects they promote protein anabolism

An excess of androgen causes virilization of the female and precocious somatic growth in children of both sexes with premature development of male sex characteristics

(4) *Other Physiological Effects of Adrenal Secretion*

Several physiological processes are effected by the adrenal secretion as a whole rather than in terms of gluco- or mineralocorticoid activity Performance of muscular work maintenance of normal blood pressure and all-round health cannot be achieved completely by any single hormone

ADRENOCORTICOTROPHIN (A C T H) AND THE ADRENAL CORTEX

The adrenal cortex deprived of its pituitary stimulus diminishes in size becomes atrophic and secretes its hormones at a greatly reduced rate The maintenance of normal cell structure and the normal rate of hormone secretion are both dependent on adequate stimulation from A C T H The anterior pituitary secretes A C T H in response to stimuli from the hypothalamus or to a falling concentration of circulating corticoids Not all the adrenal steroids partake in this interaction between circulating adrenal hormones and the pituitary indeed hydrocortisone and cortisone are the only natural hormones which have a profound effect on A C T H *release* Experimental work indicates that the pituitary secretion of A C T H is at a high level in the absence of circulating hydrocortisone while administration of this hormone in large amounts completely inhibits the release of A C T H

The pituitary *does not appear to control the rate of secretion of* aldosterone The adrenal output of this hormone appears to be related

to the state of the body's hydration and not on the serum concentration of sodium or potassium However A C T H does influence electrolyte balance by stimulating the secretion of corticosterone

Adrenal Medullary Dysfunction

As the adrenal medullae form only part of the adrenalin secreting tissue of the body their destruction is not followed by any long term physiological disturbance At the most their removal is accompanied by transient hypotension which is relieved by nor-adrenalin On the other hand chromaffin tumours of the adrenal medulla or organs of Zuckerkandl (lying beside the aorta) may secrete an excess of adrenalin and nor-adrenalin resulting in a severe disturbance of physiology

Phaeochromocytoma

This tumour commonly arises from the adrenal medulla involving the right side rather more often that the left but sometimes both It may also arise from chromaffin tissue lying beside the abdominal aorta or even in the chest or neck. The growth is seldom malignant its histology resembles the normal adrenal medulla with a network of capillaries and connective tissue separating masses of large polyhedral cells which stain brown with chromic acid The size of the tumour is very variable the majority being small and solid but cystic degeneration and areas of haemorrhage occur particularly in the larger growths

The phaeochromocytoma is not always a functioning tumour medullary growths are more likely to exhibit endocrine activity than those in extramedullary sites In the functioning growth varying proportions of adrenalin and nor-adrenalin are found but the latter usually predominates and is responsible for clinical symptoms to a greater extent than adrenalin

Clinical Manifestations

The syndrome due to a nor-adrenalin secreting tumour is extremely rare It has been observed in patients of all ages but more than half the cases have been between 20 and 50 years old Females are affected slightly more frequently than males and a familial incidence has been found on several occasions There is also an association with neurofibromatosis

The cardinal manifestation is hypertension which may be sustained or paroxysmal If the elevation of the blood pressure has been present for some time the hypertension appears to be maintained by some mechanism possibly renal which is not dependent on adrenalin because removal of the tumour does not alter the blood pressure On the other hand some

patients with hypertension indistinguishable on clinical grounds from the benign or malignant essential variety are cured by the removal of the tumour

The symptomatology of paroxysmal hypertension gives an excellent clue to the correct diagnosis but unfortunately only about one third of the cases present with such a characteristic history Attacks of hypertension are due to widespread vasoconstriction in response to an outpouring of nor-adrenalin (and adrenalin) from the tumour The onset is sudden and dramatic for the patient who experiences a sense of constriction in the chest palpitations and severe headache often accentuated by an intense feeling of fear Other symptoms are praecordial pains dizziness nausea and diarrhoea Any one symptom may be the sole manifestation of a minor attack The notable physical sign in a paroxysm is hypertension both systolic and diastolic often to an extreme degree The skin is blanched the pulse rapid being scarcely perceptible at the wrist and the pupils are dilated Although the skin temperature is lowered the body temperature may be raised and the metabolic rate increased Glycosuria with hyperglycaemia may occur The attack can last from a few minutes to several hours prolongation of the paroxysm may give rise to acute haemorrhagic retinopathy or hypertensive encephalopathy The end of an attack is heralded by a return of colour to the skin profuse sweating and a constriction of the pupils The patient gains rapid relief from his symptoms but is left weak and prostrated for some time

Diagnosis

The crux of the problem lies in the detection of the rare case of phaeochromocytoma among the many patients with essential hypertension In some instances the presence of neurofibromatosis a past history suggestive of hypertensive paroxysms or even a family history of phaeochromocytoma raise the possibility of an adrenalin secreting tumour Occasionally the tumour may be palpable and sometimes palpation in the renal area will provoke an attack of hypertension. However the only method of making sure that no case of phaeochromocytoma is missed in the presence of sustained hypertension is to subject all young hypertensive subjects without renal disease to special investigation The desirability of such a procedure might be questioned in view of the large numbers of negative investigations that must result but such a course could be justified if the test employed was specific readily available and without ill effects

If the condition presents with paroxysmal hypertension the symptoms

may be confused with migraine angina pectoris vasovagal attacks or even thyrotoxicosis These difficulties will be resolved if the patient is observed during the attack and the blood pressure recorded

Special investigations play a large part in diagnosis The most logical approach is the estimation of catechol amines (i e adrenalin or nor-adrenalin) in serum or urine by chemical or biological methods A marked increase in the serum concentration or urinary secretion of these substances is diagnostic of a functioning tumour the ratio of adrenalin to nor adrenalin being the same as in extracts of the tumour tissue As the secretory activity of the tumour varies diagnostic concentrations of catechol amines are not necessarily present at all times a difficulty which can be resolved by repeating the assay The only bar to the wide application of catechol amine estimations has been the complexity of the techniques involved However recent modifications make it very probable that a simplified procedure will not only be specific but easily available as a screening test in all suitable cases of hypertension

Other less direct approaches to the diagnosis can be divided into provocative and adrenolytic tests Firm manual pressure in the adrenal area may induce an attack of hypertension, but such a crude method is not recommended The same effect is produced by the injection of histamine or methacholine but failure to induce hypertension does not exclude the presence of a tumour A further disadvantage of any provocative test is the discomfort and even danger to which the patient is subjected when a paroxysm is induced Indeed the test should not be carried out unless an adrenolytic agent is immediately to hand so that an attack can be cut short

Adrenolytic tests involve the lowering of the blood pressure by adrenalin antagonists A prerequisite of the test is hypertension and a false negative result may be obtained if the blood pressure originally elevated by an adrenalin secreting tumour is maintained by some other mechanism Dibenamine piperoxane and phentolamine are the three adrenolytic agents which have been studied in detail Dibenamine causes a fall in blood pressure that may be dangerously prolonged in the presence of a phaeochromocytoma and may also occur in essential hypertension Piperoxane does not give these false positive results and has a short period of action but it has proved toxic to some patients The safest agent available at the moment is phentolamine the details of its use in diagnosis are recorded in the Appendix

The problem of anatomical localization follows the diagnosis of a phaeochromocytoma An intravenous pyelogram may indicate displacement of the kidney by the tumour or more accurate radiographic local-

ization can be achieved by outlining the adrenals with air which should be introduced by the presacral route direct perirenal insufflation is dangerous in that the needle may puncture the tumour A further refinement is aortography which is of limited use because of the risks from anaesthesia or from stimulation of the tumour by the needle As failure of radiographic technique to visualize a mass does not exclude the possibility of a small tumour being present some surgeons prefer exploration of the adrenals as a means of localization continuing the operation to remove the tumour when it is found The rare extramedullary tumour makes the problem more difficult as it will not be located if the adrenals are explored by the lumbar route However the most likely site for an extramedullary growth is alongside the abdominal aorta an area that can be explored together with the adrenals by a transperitoneal approach

TREATMENT

The only effective treatment is surgical removal of the tumour but it must be emphasized that this will not benefit the patient whose hypertension is no longer dependent on adrenalin Prior to operation the severity of hypertension particularly in terms of progressive retinopathy or encephalopathy may require the use of adrenolytic drugs Repeated intravenous injections of phentolamine (~10 mg) or of piperoxane (5-15 mg) will control the blood pressure and a constant intravenous infusion of these drugs can be employed Ganglion blocking agents are not effective

Before adrenolytic agents and nor-adrenalin were available operative removal of the tumour was extremely dangerous because of the violent rise in blood pressure on handling the tumour and severe hypotension after clamping the adrenal pedicle The importance of correct pharmacological control during operation is so great that it must be the sole responsibility of one man with an assistant to record the blood pressure

The choice of adrenolytic agents lies between phentolamine and piperoxane as dibenamine has a prolonged action which will interfere with the subsequent administration of nor-adrenalin Atropine in premedication potentiates the pressor effect of adrenalin and should only be used in conjunction with an injection of phentolamine Similarly ether is to be avoided as an anaesthetic chloroform ethyl chloride and cyclopropane should not be used because they may cause ventricular arhythmia in the presence of excess adrenalin. If a muscle relaxant is used gallamine is preferable to curare which has a histamine like action

Before the induction of anaesthesia a cut-down intravenous infusion

must be started keeping the vein open with a slow drip of 5 per cent dextrose (saline may embarrass the circulation) The giving set is so arranged that a bottle containing 5 per cent dextrose with nor adrenalin 4 mg /litre is ready to be run in as an alternative to the dextrose solution Hypertension is controlled by giving an adrenolytic agent into the tube of the infusion apparatus the amount given depending on the patient s response Phentolamine 5 mg i v should precede the anaesthetic and thereafter supplementary doses will be needed whenever the systolic pressure rises about 150 mg Hg (recorded every minute) The surgeon must give prior warning of handling the tumour the dissection being carried out with extreme gentleness Five minutes prior to clamping the adrenal pedicle a further warning is given so that no more phentolamine is injected Directly the pedicle is clamped the blood pressure will begin to fall and the infusion of nor-adrenalin is begun, its rate depending on the blood pressure This infusion is continued for a few hours after the patient s return to the ward The blood pressure must be recorded every 15 minutes for the first 24 hours after operation. During this time the infusion of nor-adrenalin is slowed down and brought to a stop if the blood pressure remains at a satisfactory level It is wise to keep the vein open with a dextrose drip and have nor-adrenalin immediately available in case there is a subsequent fall in blood pressure

Adrenal Cortical Failure

The major proportion of both adrenal cortices must be destroyed before failure of function becomes apparent Unilateral lesions are not accompanied by signs of adrenal insufficiency Acute destruction of the adrenals is very rare but chronic pathological processes may present with acute signs of adrenal failure precipitated by injury or infection. Bearing in mind that differences in symptomatology and treatment separate acute from chronic adrenal failure regardless of the aetiology it is wise to adopt a classification based on the underlying pathological process By this method one can distinguish

(1) *Primary Adrenal Failure*

(a) Acute lesions
Haemorrhagic (in new born)
Thrombosis of adrenal veins
Septicaemic (leading to haemorrhage)
Surgical removal of adrenals

(*b*) Chronic lesions
Tuberculosis
Idiopathic atrophy
Carcinomatous destruction *syphilis and other rare causes*

(2) *Secondary Adrenal Failure*

Lesions of anterior pituitary causing failure of adrenocorticotrophin (A C T H) secretion

ACUTE LESIONS

Spontaneous acute destruction of the adrenals is extremely rare and surgical removal of the adrenals should not give rise to acute adrenal failure because adequate hormone therapy is a prerequisite of adrena lectomy The prevention and treatment of adrenal insufficiency after operation is dealt with in a later section with a further note in the section on Cushing s syndrome on the type of adrenal failure which may follow subtotal adrenalectomy in this disease (see page 105)

(*a*) *Adrenal Haemorrhage in the New-Born*

Massive bilateral haemorrhagic destruction is facilitated by the rapid involution of the cortex that occurs normally after birth Asphyxia during or after labour is probably the precipitating factor Symptoms develop a few hours or days after birth leading to extreme prostration lividity of the extremities feeble pulse and convulsions Generalized purpura may be present the condition is rapidly fatal but fortunately of great rarity

(*b*) *Waterhouse-Friderichsen Syndrome*

In children acute septicaemia usually of meningococcal origin may be associated with generalized purpura and haemorrhagic destruction of the adrenals The onset is fulminant the extremely toxic state engendered by the causative organism being complicated by acute adrenal failure Headache vomiting abdominal pain and often diarrhoea are followed by delirium which gives way to coma Peripheral circulatory collapse is marked and the temperature after reaching 105 or 106 , falls to subnormal levels as death supervenes Strenuous treatment with antibiotics and adrenal hormones may save life but often the infection is so overwhelming that no therapy is of avail

(c) Bilateral Thrombosis of Adrenal Veins

The cause of the thrombosis is unknown It occurs in adult life usually associated with pregnancy or following severe burns but sometimes in apparently healthy people Abdominal pain is the main feature associated with persistent vomiting The pain is severe and continuous located in the epigastrium or under the right costal margin, but seldom in the loin and always without muscular rigidity There is a surprising absence of collapse but pulmonary oedema heralds the fatal termination The appropriate treatment is similar to that for an Addisonian crisis (see page 94)

Chronic Adrenal Lesion Addison's Disease

The origins of modern endocrinology stem largely from Thomas Addison s description of the disease that bears his name In 1855 he reported a condition of languor debility feeble action of the heart and skin pigmentation which he associated correctly with bilateral adrenal destruction found at autopsy

Pathology

In the past tuberculosis was the cause of about 80 per cent of Addison s disease idiopathic atrophy accounting for most of the other cases The decline in the incidence of tuberculosis in this country has led to the present position in which idiopathic atrophy is as common as tuberculosis in chronic adrenal failure Other causes such as metastatic carcinoma syphilitic fibrosis or amyloidosis are very rare

Tuberculosis destroys both the cortex and the medulla of the adrenal The lesion varies from massive caseation to the proliferative type with many tubercles and fibroblasts Calcification is rare It is remarkable that the histological picture is always one of active tuberculosis even when all other foci of the disease appear to be healed

Idiopathic atrophy is of unknown aetiology in some instances there is a familial incidence of the disease In contrast to tuberculosis the medulla is unaffected despite complete atrophy of the cortex Necrosis of the cells reduces the cortex to the thinness of paper Some fibrosis occurs and the cortex shows considerable infiltration with lymphocytes which distinguishes idiopathic atrophy from the atrophic cortex due to pituitary failure It is of interest that the thyroid shows histological evidence of atrophy in many cases of idiopathic atrophy of the adrenal but not in cases of tuberculous destruction Occasionally there is clinical evidence of hypothyroidism

CLINICAL

Addison's disease is rare It can occur at any age but its maximum incidence lies in the fourth and fifth decade Children are seldom affected This disease is of world-wide distribution and the sexes are equally prone to its development

The onset is usually insidious but the untreated disease is inevitably fatal the tempo of its progress being varied by acute episodes Sometimes there are no premonitory symptoms and the clinical presentation is in the acute form of an Addisonian crisis However the symptomatology of the chronic form is related to that of the crisis variations in the clinical picture indicating that the disturbance of physiology is not uniform in all patients Symptoms and signs fall into related groups as follows

Asthenia

A profound lethargy envelops the patient Muscular fatigue after exertion is linked with a disinclination to undertake the daily routine Later actual muscle weakness occurs which is so marked in a crisis that the patient cannot lift his head from the pillow In this state muscle cramps are common

Gastro-Intestinal

Anorexia and vague dyspepsia are early symptoms A distaste for fatty foods may simulate gall bladder disease in rare instances salt-craving may suggest the correct diagnosis Vomiting is ominous usually heralding a crisis when persistent vomiting is associated with generalized abdominal pain and often diarrhoea

Cardiovascular

Hypotension gives rise to faintness particularly when the patient has been standing for some time Diminished cardiac reserve causes dyspnoea on exertion although this is not a dominant symptom Profound peripheral vascular collapse is characteristic of a crisis

Hypoglycaemia

Frank symptoms of hypoglycaemia are relatively rare Mental confusion dizziness visual disturbance or diplopia are likely to arise in the early morning when the patient has been fasting or after strenuous exercise without food It is important to remember that one cause of coma during an Addisonian crisis is hypoglycaemia This tends to be forgotten the patient receiving saline intravenously but no glucose until severe hypoglycaemia has developed

ADRENAL INSUFFICIENCY

	Asthenia	Gastro-intestinal	Vascular	Blood Sugar	Sex
Chronic	Lethargy* Fatigue+‡ Weakness+	Anorexia‡ Dyspepsia	Fainting+*	Dizziness Confusion	Loss of Libido Amenorrhoea
	Failure to respond to infection/trauma‡				
Acute	Prostration+ Cramps+	Vomiting+ Abdominal pain Diarrhoea	Collapse Pulseless	Coma*	
	Dehydration. Loss of weight Serum Na↓ K↑ Haematocrit↑ Urine Cl+			FBS↓ STT flat	17 K.S↓

Glucocorticoid = *
Mineralocorticoid = +

Sex

Loss of libido is common to both sexes and in women amenorrhoea is the rule but does not usually occur until the patient s general health has deteriorated

Resistance to Stress

The patient s life is at the mercy of minor infections or traumata which would do no more than annoy a healthy person Prostration or delayed recovery from everyday infections is a symptom suggestive of chronic adrenal failure

An important aspect of this failure to adjust to environmental changes is the severe clinical disturbance which results from relatively minor deviations from normal electrolyte equilibrium or blood-sugar concentration For this reason chemical evidence of adrenal insufficiency does not show the gross changes expected from the clinical picture

Miscellaneous

The metabolic rate is lowered by a lack of adrenocortical hormones and many patients are intolerant of cold weather Generalized aches and pains of an arthralgic type are very common and relieved dramatically by hormonal replacement therapy Although the prevailing mood of a patient with Addison s disease is one of apathy and depression, the disease can present with evidence of acute mania an ominous sign for the restlessness it induces will aggravate the physical weakness

PHYSICAL SIGNS

Pigmentation

A dirty brown pigmentation over the body is characteristic of Addison's disease its suggestion of healthy sun-tan contrasting with the weakness and lethargy of the patient The pigmentation is maximal over the *exposed parts of the body but is also accentuated in areas under pressure* from clothing such as the axilla and those parts like the areola of the breast which are normally pigmented In addition to the diffuse pigmentation small jet black pigmented spots or freckles are frequently seen Occasionally areas of vitiligo contrast with the brown skin Pigmentation is also present in recent scars The backs of the fingers are often so heavily pigmented with the typical dirty grey brown colour that the patient is forever washing his hands in a vain attempt to clean them In the palm of the hand pigmentation of the creases is common, and in the mouth by the lip margin or the mucosa of the cheek or palate the pigmentation is also found but is commonly of a blue ink-stain type Similar blue spots of pigmentation are found on the labia but not in the vagina

The degree of pigmentation depends on the duration of adrenal failure and the natural colouration of the skin It is seldom marked if the onset of the disease is acute and usually takes several months to develop It is more obvious in brunettes than blondes but cannot be distinguished against the normal colouration of the dark skinned races although the blue pigmentation of the buccal mucosa retains its diagnostic significance at all times Sunshine increases the pigmentation but there is little fading during the winter

The pigmentation is due to melanin but the mechanism of its deposition has been a problem for a long time The old theory is that dioxyphenylalanine which may be a precursor of adrenalin is not converted to this substance but becomes fixed in the skin as melanin More recent work makes it probable that the pigmentation is influenced by an excessive secretion of intermedin the melanophore expanding hormone which has a close chemical association with A C T H Cortisone inhibits the excessive production of A C T H in Addison's disease and diminishes the pigmentation

Loss of Weight

As the disease progresses loss of weight mainly as a result of anorexia becomes marked and is accentuated by dehydration.

Cardiovascular Changes

A remarkably feeble action of the pulse was noted by Addison and is

still an important sign being present when there is no significant hypotension However a lowering of the blood pressure is a major feature in severe cases the systolic pressure seldom rising above 100 mg Hg The blood pressure should be recorded with the patient erect as well as lying down because postural hypotension is often observed The heart sounds are faint and the size of heart demonstrated radiographically is greatly diminished by virtue of reduced blood volume and actual atrophy of the myocardium

Electrocardiographic changes mainly consisting of depression of the T wave are found frequently but are not specific Restoration to normality may depend on correction of the electrolyte disturbance but the action of cortisone is usually required for complete normality

Miscellaneous

Apart from pigmentation the skin is often abnormal in its peculiar fineness of texture associated in women with an absence of hair Hair growth of scalp axilla and pubis is normal in men due to the adequate amount of androgen derived from the testis but the absence of adrenal androgens results in a loss of axillary and pubic hair (with normal scalp hair) in women

Addisonian Crisis

This acute episode is precipitated by infection trauma or salt loss from vomiting or excessive sweating The precipitating factor may be quite minor in itself but it sets off a disturbance of such severity that life is always threatened and sometimes extinguished

Muscular weakness increases rapidly until the slightest effort becomes impossible Vomiting is persistent the fluid loss being aggravated by diarrhoea Abdominal pain, sometimes with a marked rigidity is severe enough to mimic an acute abdominal catastrophe The skin becomes cold and inelastic from dehydration and the body temperature falls The radial pulse is imperceptible the blood pressure unreadable and the heart sounds scarcely audible The profound peripheral vascular collapse lends a cyanotic tinge to the extremities and the fall in glomerular filtration rate may result in anuria A curious feature is the not infrequent occurrence of hyperpyrexia when the patient is being resuscitated with intravenous fluids

DIAGNOSIS

Tiredness is so universal a symptom that the rare instance of languor and fatigue from Addison s disease may be overlooked Alternatively

the persistent complaints of the chronic neurotic can suggest adrenal failure but the absence of pigmentation and the variability of the symptom indicate the correct diagnosis Greater difficulties arise with certain organic conditions

Steatorrhoea

Malabsorption by the small intestine leads to loss of weight fatigue and often some degree of hypotension together with a brown pigmentation of the body Diarrhoea may be absent and vague dyspeptic symptoms give a false suggestion of chronic adrenal failure Absence of buccal pigmentation is a point against adrenal failure However final diagnosis depends on special tests particularly a fat balance to demonstrate steatorrhoea with considerable care in their interpretation because in steatorrhoea the glucose tolerance curve is flat and slow absorption leads to failure of diuresis after a water load

Tuberculosis

As Addison s disease can co-exist with active tuberculosis in extra-adrenal sites thus can be a serious problem of differential diagnosis Apart from the symptoms of tuberculosis the loss of weight and even some darkening of the skin can falsely suggest adrenal involvement A good *clinical response to chemotherapy may make it clear that the symptoms* were due solely to tuberculosis but the doubt in some cases can only be resolved by special investigations

Pernicious Anaemia

Addison himself was confused initially between the anaemia named after him and the clinical picture of adrenal failure because of the similarity of the symptoms and the cafe au lait tint of the skin in pernicious anaemia Haematological investigation solves the problem

Panhypopituitarism

The presence of pigmentation distinguishes primary from secondary adrenal failure Body hair is sparse in women with Addison s disease but is not absent as is usual in panhypopituitarism

Gastro-Intestinal Disturbances

Occasionally the abdominal symptoms of Addison s disease together with browning of the skin give a superficial resemblance to chronic gall bladder disease In an Addisonian crisis the recurrent vomiting diarrhoea and abdominal pain closely simulate acute gastro-enteritis but the cardinal point of difference is the presence of urinary chlorides despite obvious dehydration and body chloride depletion The abdominal

pain and rigidity in a crisis can mimic an acute abdominal condition such as a perforated peptic ulcer and peritonitis

No one test is diagnostic of adrenal failure The clinical picture is of greater importance than special investigations which require the correlation of various results before interpretation.

Provocation of an Addisonian crisis by depriving the patient of salt should never be considered because it is likely that the patient will not survive to hear that the diagnosis has been made Despite the physiological importance of the electrolyte disturbance serum sodium and potassium concentrations remain within normal limits unless the patient is in a severe crisis A small fall in serum sodium and rise in serum potassium may become apparent by determination of the sodium/potassium ratio of the serum A further attempt to analyse the electrolyte disturbance is the Kepler test which measures the diuresis of chloride retention of urea and failure of water elimination that occurs in adrenal failure An analysis of this test in the Appendix will indicate that there are several limitations to its diagnostic value

The availability of A C T H has made it possible to test the adrenal response to this hormone a procedure which is safe and of great value in diagnosis There is some doubt as to the best index of adrenal response and the necessary duration of A C T H stimulation The drop in circulating eosinophils four hours after one injection of A C T H has been widely used but is not fully reliable More prolonged stimulation either by slow intravenous infusion or an intramuscular injection of long-acting A C T H-gel is preferable the adrenal response being measured in terms of blood corticoids or their urinary metabolites Such methods are complicated from the laboratory point of view but of considerable value Failure to elicit adequate adrenal response is a clear indication of primary adrenocortical failure

TREATMENT

The phases of treatment are divisible into measures to overcome an Addisonian crisis those for maintenance therapy and those designed to prevent the onset of crisis

The number of therapeutic weapons is increasing but the newer steroid compounds are very similar in action to those readily available All types of treatment rely on the following preparations

(1) *Adequate Sodium Chloride*

Available for oral use in addition to dietary salt or for intravenous infusion

(2) *Aqueous Adrenal Extracts*

These are mainly mineralocorticoid in activity but lack the potency of pure steroid preparations and are deficient in glucocorticoid activity They are given by intramuscular or intravenous injection.

(3) *Deoxycorticosterone Acetate* (*D O C A*)

This is a potent synthetic mineralocorticoid which does not form part of adrenocortical secretion. Large doses will cause excessive sodium retention, oedema and hypertension Many preparations are available for daily intramuscular injection, implantation as pellets and as the trimethylacetate which gives long term action from one intramuscular injection

(4) *Cortisone Acetate*

This is of great importance as a glucocorticoid and for the effect it has in increasing the patient s resistance to stress Its mineralocorticoid activity is very low It may be given as a daily intramuscular injection but has the great advantage of being more rapidly active on oral administration in tablet form.

(5) *Hydrocortisone*

Its action is similar to cortisone and is also potent on oral administration. It is available in alcoholic solution for intravenous injection. By this route its action is immediate but its destruction is very rapid, necessitating a continuous slow infusion.

Treatment of Addisonian Crisis

This dangerous emergency requires the best nursing care adequate replacement of fluid and electrolyte loss correct administration of gluco- and mineralocorticoids and suppression of any infective process

The basic nursing instructions can be summarized as

Lay the patient flat and keep him well covered Prevent any exertion by anticipating the patient s needs, remembering the danger of inhaled vomit. Never disturb the patient unnecessarily record the blood pressure and pulse every fifteen minutes and the temperature every half hour

Vomiting precludes fluid replacement by mouth and necessitates intravenous infusion cutting down on a vein is to be deplored as patent veins are of inestimable value to the patient s future Normal saline is the correct fluid for initial replacement of sodium and water loss but it is difficult to judge the amount required. The degree of prostration and circulatory collapse is not directly related to the amount of electrolyte depletion and usually suggests a far greater electrolyte disturbance than is

the case Furthermore it is extremely easy to overload the circulation so that the speed of infusion must be slow and the amount infused kept to a minimum In practice one to two litres of normal saline suffices in the great majority of cases maintenance of electrolyte balance then depends on the slow infusion of 1/5 normal saline with 4 per cent dextrose to offset the possibility of hypoglycaemia.

Injection into the tube of the infusion apparatus provides a quick and easy method of hormone administration Salt retaining corticoids may be provided by 10-20 c c of aqueous adrenal extract injected in this manner the dose being repeated every 4-6 hours while the infusion continues

However adrenal extracts have been almost superseded by the introduction of pure glucocorticoids which have greatly enhanced the efficiency of treatment and should be used in all cases An initial intravenous *injection of 50 mg hydrocortisone (prepared in alcoholic solution for this route)* may be sufficient *in itself* but can be reinforced by introducing hydrocortisone into the bottle of infusion fluid in a concentration that will deliver 10 mg per hour into the vein As an alternative cortisone acetate 100 mg intramuscularly given at the outset will provide adequate glucocorticoid activity for milder cases the injection being repeated every eight hours with gradual reduction of the dose to 50 mg However its speed of action is relatively slow and it does not supplant the initial intravenous dose of hydrocortisone which is necessary for quick action in the more severe cases Deoxycorticosterone (D O C) is not required in the treatment of crisis indeed it has definite dangers in terms of excess sodium retention giving rise to heart failure

If any source of infection is discovered as the precipitating factor of the crisis then appropriate chemotherapy should be started at once In the absence of any obvious infection prophylactic penicillin should be administered as a routine It must be remembered that treatment with glucose saline and mineralocorticoids alone may be associated with considerable pyrexia of metabolic rather than infective origin However this phenomenon does not occur if adequate glucocorticoid hormones have been given

Therapy for Total Adrenalectomy

The regime for total removal of normally functioning adrenals is not applicable to the operative treatment of Cushing s syndrome the special problems of which are discussed in a later section (see page 105)

Cortisone alone provides a satisfactory replacement therapy over the time of operation because post-operative salt retention will take place in

the absence of strong mineralocorticoids Oral dosage is obviously unsatisfactory under the conditions of operation and the first intramuscular dose must be given some time prior to adrenalectomy as absorption is slow Satisfactory results are obtained with cortisone acetate 40-50 mg injected twice daily starting three days prior to operation and continuing until the fourth or fifth post-operative day There is no need to increase this dose on the day of operation at the end of the course oral cortisone 25 mg twice daily should be started

Electrolyte balance is controlled most easily by giving a constant intake of NaCl 8-10 grams per day Prior to operation this amount will be present in the patient s diet but may have to be added to the food if only a light diet is tolerated Directly after operation, saline given intravenously will provide the correct amount of sodium As the daily requirements of water are 2000 to 2500 ml the correct volume of fluid administered intravenously and the correct NaCl intake has to be adjusted by varying the proportions of normal saline 1/5 normal saline with 4 per cent dextrose and 5 per cent dextrose without saline

No other therapy is required as a routine but a supply of nor-adrenalin and hydrocortisone must be available for emergency during the first 36 hours after operation Hypotension during this period usually responds to methedrine 5-15 mg given intramuscularly or intravenously but if it persists nor-adrenalin 4 mg per litre of fluid is given as a continuous intravenous infusion 50 mg of intravenous hydrocortisone should be given if the patient s general condition becomes very poor However the adequate pre-operative dosage of cortisone makes the possibility of post operative crisis remote

MAINTENANCE THERAPY

This applies to all cases where crisis has been treated satisfactorily and to those whose symptoms do not warrant a more active form of therapy

The evolution of treatment for chronic adrenal insufficiency has passed through the stages of high salt diets and aqueous adrenal extracts to various preparations of the synthetic deoxycorticosterone and finally to their combination with cortisone Further advances are likely in the field of synthetic steroid chemistry to provide one steroid with adequate salt-retaining and glucocorticoid activity At the moment correct therapy may be attained by initial treatment with D O C A adding cortisone as required at a later date or by initial administration of cortisone adding D O C A if electrolyte balance is not maintained.

D O C A for long-term treatment is best employed as a tablet implanted

below the skin of the abdomen and designed to exert sufficient activity for six months Before implantation is considered the patient's electrolyte balance must have been brought to normal levels by daily intramuscular injections of D O C A associated with a constant salt intake which is easily obtained by adding 3-4 grams of NaCl to a normal diet The usual requirements of D O C A given daily by intramuscular injection lie between 2-5 mg The correct dose depends on restoration of weight alleviation of hypotension and avoidance of oedema as well as normal serum electrolyte concentrations The injections should be continued for at least three weeks if mistakes in the size of the eventual implants are to be avoided As a general guide 100 mg of D O C A by implantation is needed for every 1 mg required on daily injection. This scheme is more likely to over-estimate the size of implant so that it is wise to set an upper limit of 400 mg of D O C A for any implantation

Intramuscular D O C A should be continued in decreasing dosage for the first few days after implantation If this implant proves excessive as judged by oedema and hypertension, the patient must cease to take the additional salt In brief the initial dose of D O C A is determined with a constant salt intake but after implantation the dose of hormone is constant and the salt intake may be varied. It is foolish to wait until signs of adrenal failure recur before considering re-implantation far better to renew the implant every six or seven months

An alternative method of depot therapy is provided by the cystalline suspension of deoxycorticosterone trimethylacetate given by deep intramuscular injection. One injection lasts 3-4 weeks 25 mg being roughly equivalent to 1 mg of the ordinary D O C A administered daily A new mineralocorticoid Fluorohydrocortisone may supersede this as it will control electrolyte balance in an oral dose of 0 25 to 1 0 mg daily

Restoration of electrolyte balance seldom frees the patient of all his symptoms Capacity for manual work and resistance to fatigue remain diminished For this the oral administrations of cortisone 12 5 to 25 mg per day is required

Cortisone as the sole hormone administered requires additional salt in the diet if sodium balance is to be maintained An oral dose of cortisone acetate 12 5 mg twice or three times a day together with NaCl 3-9 grams added to a normal diet is an extremely efficient form of treatment Only a few cases will require D O C A as well The disadvantages of oral cortisone is apparent immediately the patient vomits an event which demands a swift change to the intramuscular route

Cortisone in the dosage required for replacement therapy does not adversely affect tuberculosis and the hormone can be used with safety in cases of tuberculous Addison s disease

At all times the patient with chronic adrenal failure is in danger of a crisis despite the most adequate maintenance therapy Trauma infection or even extreme exertion are the common occasions of severe adrenal insufficiency which must be avoided if possible or treated immediately with an increased dose of cortisone An additional 100 mg of cortisone intramuscularly is a good precautionary dose The avoidance of crisis requires constant unobtrusive medical supervision which does not alarm the patient but invites his co-operation

Adrenocortical Hyperfunction

The adrenal cortex may secrete an excessive quantity of its normal secretion or an excess of one hormone The accompanying anatomical changes may be either tumour formation benign or malignant or bilateral cortical hyperplasia it is generally accepted that secreting tumours are autonomous in function and that hyperplastic adrenals are stimulated by the anterior pituitary s secretion of A C T H As tumours produce disturbances of function similar to those of hyperplastic adrenals a classification of syndromes according to physiology is preferred to one based on histology

(1) *Excessive Glucocorticoid Secretion*
 Cushing s syndrome
 (also induced by administration of excess A C T H and mimicked by excessive cortisone therapy)

(2) *Excessive sex hormone secretion*
 (*a*) Androgens
 (1) Virilism in females
 (2) Precocious pseudopuberty in boys
 (*b*) Oestrogens
 Feminizing tumours in males

(3) *Excessive mineralocorticoid production*
 (Primary aldosteronism)

Cushing s syndrome in which the effects of glucocorticoids predominate is the clinical example of an excessive adrenal secretion of normal constitution Hence this syndrome can be induced by administering large amounts of A C T H The other syndromes listed are examples of

excessive production of one type of hormone Adrenal virilism is not uncommon but feminization of the male is extremely rare and always due to tumour formation Primary aldosteronism is a newly discovered syndrome and therefore its frequency cannot be assessed as yet

Cushing s Syndrome

The eponym is retained because there is no precise physiological term to indicate the diagnosis The name is applied to the clinical condition as described by Cushing but does not indicate an acceptance of his views on the aetiology of the condition

PATHOLOGICAL PHYSIOLOGY

The clinical syndrome as described by Cushing was thought to be a pluriglandular disease until the identical clinical picture was produced by the prolonged administration of excessive doses of A C T H to patients without adrenal disease The contribution of hydrocortisone and cortisone to the disturbance became obvious when the identical syndrome developed after high dosage of these substances and raised levels of 17 hydroxycorticoids were found in cases of spontaneous Cushing s syndrome

In physiological terms Cushing s syndrome is due to an excessive secretion of the normal hormone from the adrenal cortex Some cases are associated with tumours of the adrenal but the majority occur with bilateral hyperplasia of the adrenal cortex probably due to an increased output of adrenocorticotrophin from the anterior pituitary The clinical evidence for increased pituitary function in these cases is based primarily on the fact that adrenocortical hyperfunction is reduced by inhibiting the pituitary Cushing s original histological findings of small basophil tumours in the pituitary did not as he thought prove the pituitary origin of the disturbance because such tumours are not present in all cases of the syndrome and are a common autopsy finding in the absence of endocrine disturbance However one histological feature of the pituitary which is common to all cases including those with an adrenal tumour is hyalinization of the basophil cells This hyaline change described by Crooke is not present in all the cells but the number of cells involved is roughly proportionate to the activity of the endocrine disturbance The significance of the change has been hotly debated but it has recently been described in patients treated with cortisone and A C T H The consensus of opinion is that hyalinization of the basophils does not indicate increased pituitary function but is due to a high level of circulating glucocorticoids

Cortisone in the dosage required for replacement therapy does not adversely affect tuberculosis and the hormone can be used with safety in cases of tuberculous Addison s disease

At all times the patient with chronic adrenal failure is in danger of a crisis despite the most adequate maintenance therapy Trauma infection or even extreme exertion are the common occasions of severe adrenal insufficiency which must be avoided if possible or treated immediately with an increased dose of cortisone An additional 100 mg of cortisone intramuscularly is a good precautionary dose The avoidance of crisis requires constant unobtrusive medical supervision which does not alarm the patient but invites his co-operation

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out of proportion to the degree of fatty distention They are a dull purple colour similar to the face covering the body with broad livid stripes The texture of the skin on the trunk particularly over the back is roughened with hyperkeratosis and some increase of coarse short hair Profuse and odorous sweating affects the axillae and other parts of the body The face is unduly greasy and the scalp hair lustreless and often thinned

The livid discolouration and plethoric appearance of the patient is seldom associated with significant polycythaemia but is due to capillary dilation and stasis It is reminiscent of the flush that suffuses the previously chalk white face of the patient with panhypopituitarism who is given large amounts of cortisone The peripheral vascular stasis is often complicated by indolent cellulitis persistent fungus infection of the feet and thrombophlebitis with the appearance of ulcers on the lower leg Purpura and spontaneous ecchymoses are further evidence of connective tissue disturbance which is also illustrated by the failure of skin healing and granulation after injury

In women both acne and facial hirsutes are seen This does not necessarily indicate an increased adrenal secretion of androgens as the skin reaction to hydrocortisone varies with age Thus acne is common in adolescents with Cushing s syndrome and facial hirsutes mainly seen in menopausal cases However the adrenal secretion may contain an increased proportion of androgen which gives rise to amenorrhoea, male type body hair and may offset the characteristic muscle wasting and weakness of excessive hydrocortisone

The locomotor system is affected both in muscle and in bone Wasting and weakness of muscles with increased fatigue is common Muscle tone is diminished The skeleton is osteoporotic mainly in the spine and spontaneous fractures of ribs or vertebrae are not uncommon

Hypertension is an important sign because the course of the disease is often dominated by this disturbance leading to death in hypertensive heart failure or from renal failure The elevation of the blood pressure gradually increases and malignant hypertension with papilloedema and albuminuria can occur

Electrolyte disturbances are seldom obvious but may contribute to muscle weakness and hypertension The bloated appearance of the patient with the skin indented by tight clothing suggests some water retention but demonstrable pitting oedema is rare in the absence of heart failure Serum sodium concentration is at the upper limit of normality but the serum potassium is often abnormally low associated with a raised serum

Although the physiological basis of Cushing s syndrome can be ascribed to adrenocortical hyperfunction the anatomical lesions are of importance in terms of treatment and prognosis Tumours of the adrenal cortex associated with the syndrome are usually benign adenomas but may be malignant with widespread metastases It is important to remember that the adrenal on the opposite side to the tumour is almost invariably atrophic and functionless leading to severe but temporary adrenal insufficiency after surgical removal of the tumour In rare instances Cushing s syndrome is associated with a neoplasm of the pituitary which causes expansion and erosion of the sella turcica Such tumours are not composed solely of basophil cells but contain many chromophobe cells or even acidophils In the latter case acromegaly is associated with adrenal hyperfunction Lastly neoplasms of the thymus and bronchus have been reported in Cushing s syndrome but they are associated lesions and are not concerned with the aetiology of the disease

CLINICAL PICTURE

Cushing s syndrome is a rare condition usually occurring between the ages of 20 to 40 years It is seen in childhood when it is almost invariably *associated with an adrenal tumour In adult cases about one in four* have an adrenal tumour Women are affected twice as commonly as men The onset is not infrequently associated with pregnancy but may arise in late puberty or occasionally at the menopause

The fully developed syndrome presents such a striking appearance that the diagnosis is revealed immediately With some truth it has been called Humpty-Dumpty disease describing the typical habitus Obesity is an important feature not in its degree which is usually moderate but in its distribution The face is grossly fat with a marked plethora the bulging cheeks give a rotund contour often described as moon-faced and the mouth pouts like a sunfish The trunk is also obese with an accentuation of adipose tissue in the abdominal wall and a pad of fat over the upper thoracic vertebra the buffalo hump In contrast to the face which gives the impression of enormous weight gain the limbs are thin with muscle wasting Seen in profile the patient has a fat face a rounded back from kyphosis as well as an upper thoracic pad of fat a protuberant abdomen and spindly legs

The skin is affected in several ways The plethora of the face is matched by purple discolouration of the lower leg The trunk is disfigured by striae distensae over the axillae buttocks abdomen and upper thighs These striae are remarkable for their great length and breadth which is

DIAGNOSIS

The diagnosis is still made on clinical grounds the physical signs and their emergence in a composite picture being more important than any biochemical test. The identification of the disorder of function must be followed by the discovery of the anatomical lesion

Cushing s syndrome is rare but a number of patients present one or more features rather reminiscent of the condition Fat adolescent girls with acne irregular menstruation and a few narrow pink striae on the abdomen suggest adrenal hyperfunction but the habitus is not similar to Cushing s syndrome and a balanced reducing diet alters the girls contours and leads to a change in the complexion. At the menopause some facial hirsutes or red face obesity and mild diabetes with or without hypertension is not uncommon But these features seldom arise together and are not progressive However there are some patients with the stigma of Cushing s syndrome without gross constitutional disturbance this may be termed benign transient hyperfunction of the adrenal cortex because the condition settles spontaneously The only way to make this diagnosis is to observe the patient carefully over a period of months until the condition has disappeared as compared to the progression of Cushing s syndrome As hypertension is so important in the development of Cushing s syndrome serial records of blood pressure are a necessity in all patients

Aids to diagnosis include a glucose tolerance test and determination of serum sodium potassium and bicarbonate The typical disturbance of Cushing s syndrome is impaired carbohydrate tolerance with a lowered serum potassium and a raised bicarbonate X-ray of spine and ribs is required to detect osteoporosis or spontaneous fractures Available methods of steroid estimation are a considerable help in determining the activity of the adrenal cortex at the time of examination, but must always be considered in terms of the clinical picture and are not diagnostic in themselves The urinary excretion of 17 ketosteroids reflects the androgen secretion of the adrenal and is therefore not an aid to diagnosis 17 hydroxycorticoids in blood or urine and 17 ketogenic steroids in urine are increased being of diagnostic importance in that they reflect adrenal glucocorticoid production.

The determination of the anatomical lesion is a radiological problem An X-ray of skull should be a routine procedure to exclude the rare case with a large adenoma of pituitary The presence or absence of an adrenal tumour is shown best by outlining the adrenals with air introduced by the presacral route This technique may be combined with visualization of

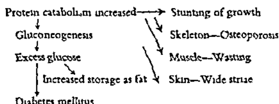
bicarbonate and lowered serum chloride This hypokalaemic alkalosis can be corrected by the administration of potassium salts

Impaired glucose tolerance is the rule sometimes with a mild insulin resistant diabetes There is seldom any tendency for this diabetes to proceed to ketosis The presence of diabetes adds to the risks of skin infections and vulvitis

Loss of libido i common to both sexes Irregular menstruation sometimes with menorrhagia is followed by amenorrhoea Although increased facial hair and loss of scalp hair suggests virilism there is no enlargement of the clitoris and no atrophy of the lower genital tract

Some degree of mental disturbance is common Frank psychosis is not infrequent and indeed may dominate the problems of treatment The reason for this is obscure but similar psychotic episodes have been noted in patients treated with A C T H or cortisone

Some of the rather bizarre physical signs of Cushing s syndrome can be linked together on the basis of the protein catabolic action of cortisone Perhaps this is illustrated best by the cessation of growth and consequent dwarfism in children suffering from this disease The accompanying table illustrates the effect of increased protein breakdown on the clinical picture



NATURAL HISTORY

Changing appearance and increasing weight may lead the patient to seek medical advice Backache and fatigue together with physical weakness are symptoms that progress gradually but may be the presenting feature It is rare for thirst and polyuria to be severe enough for the patient to complain about them On the other hand headaches associated with hypertension, can be the main complaint On the whole a general feeling of illness and lethargy accompanies the change in appearance and leads to a visit to the doctor

The prognosis in the untreated disease is poor death occurring from hypertension infection or severe psychosis within five years of the onset However a few patients particularly young men develop a mild form of the disease with spontaneous remission

followed by resection of the opposite adrenal and the atrophic gland will be left alone as it indicates the presence of a tumour in the opposite adrenal An anterior transperitoneal approach allows the inspection of both adrenals after one incision but subsequent adrenalectomy entails a formidable amount of dissection

Medical preparation for adrenalectomy is all important Correction of potassium deficiency by administering potassium salts orally and a high protein diet are essential If diabetes mellitus is present the administration of insulin will be an aid to protein anabolism The abrupt fall in circulating corticoids from an abnormally high level has to be prevented by the administration of cortisone in large doses 100 mg of cortisone acetate i m should be given twice daily for the two days prior to operation On the day of operation 200 mg of cortisone twice daily is required and a supply of hydrocortisone for intravenous infusion made ready for immediate use in case the patient s condition suddenly deteriorates Following operation the dosage of cortisone is reduced each day until it is stopped about the third post-operative week. A gradual progressive diminution in dose is essential If the remaining adrenal tissue fails to function at this time adrenal insufficiency is heralded by extreme anorexia lethargy and vague aches all over the body Demonstrable electrolyte changes are rare and hypotension is not an invariable sign These symptoms require an immediate resumption of cortisone therapy to be accompanied by the injection of A C T H (50 mg daily of a long acting preparation) to stimulate the remaining adrenal tissue It must be remembered that extreme atrophy of the adrenal on the opposite side to a tumour which has caused Cushing s syndrome may result in prolonged adrenal insufficiency occasionally lasting for months after removal of the tumour The long long term therapy after total adrenalectomy is similar to that for Addison s disease

Excessive Androgen Production

Congenital Adrenal Hyperplasia with Androgenic Excess

This syndrome is often described as two separate entities female adrenal pseudohermaphroditism and male adrenal precocious pseudopuberty The difference lies only in the type of sex development induced in either genetic sex but the aetiology of the condition is common to both sexes

Pathological Physiology

The disturbance is congenital and familial The condition is far more common in females than in males (four female to one male case) but

the kidneys by intravenous or retrograde pyelography Such investigations are uncomfortable to the patient and the results are equivocal in many cases Some surgeons prefer a straight X-ray of abdomen which may reveal a tumour followed by exploratory laparotomy In that the treatment of Cushing s syndrome is now based on bilateral subtotal adrenalectomy for the cases with hyperplastic adrenals there is much to recommend this direct approach as a decision to operate on the adrenals depends on the severity of the disease and not solely on the presence of an adrenal tumour

TREATMENT

The presence of an adrenal tumour is an absolute indication for operative removal In other cases pituitary activity can be suppressed by deep X-rav therapy or radon seed implantation, or adrenal hyperactivity curbed by resecting these glands

The long term results of pituitary suppression have proved disappointing Radon seed implantation into the pituitary is not without danger and has li tle to recommend it Deep X-ray therapy provided it is not repeated without regard to radionecrosis of the brain is a safe and reasonable form of treatment for milder cases when the major operation of adrenalectomy is considered to be unwarranted

Subtotal adrenalectomy is undoubtedly the treatment of choice in all cases where the disturbance of function is likely to threaten life The adrenals must be considered as one functional unit the aim as in thyroidectomy for thyrotoxicosis is to cut down the amount of functioning tissue by 8 to 9 tenths Consequently unilateral adrenalectomy is not sufficient to control the disease but if the patient s general condition is poor removal of one adrenal can be followed at a later date by resection of the other If the remaining adrenal tissue is not viable the patient is left in a totally adrenalectomized state However very small surviving adrenal remnants in patients under -5 years old may hypertrophy and cause a relapse of Cushing s syndrome, such a narrow margin between adrenal insufficiency and relapse makes total adrenalectomy advisable Older patients are less likely to relapse so 20 per cent of one adrenal should be preserved

The lumbar route is to be preferred for exploration of the adrenals In the absence of positive radiological evidence of a tumour there is nothing to guide the surgeon in his choice of which side to explore first Exposure of the adrenal will reveal a tumour a hyperplastic gland, or an atrophied one A tumour will be removed a hyperplastic gland removed

on to it or the vagina and urethra have separate orifices in the normal female manner

Virilization proceeds throughout childhood The clitoris continues its growth and is often erectile Pubic hair then axillary hair appears about the age of 5 years Later at about 8-12 years of age acne and facial hirsutes appear The growth of face hair becomes so strong that frequent shaving is required and hair grows luxuriantly over the chest and limbs Recession of the frontal scalp hair can proceed later to a male type baldness The pubic hair grows upwards to the umbilicus The breasts remain undeveloped and amenorrhoea is the rule Very occasionally a uterine bleed occurs presumably because the adrenal is secreting a quantity of oestrogen as well as androgen

In some cases the enlargement of clitoris is of a lesser degree which escapes notice in infancy and the appearance of body hair at the age of 4 to 6 years is the first observed sign of sex disorder These patients present a problem in diagnosis which lies between an acquired virilism and the congenital type

The Male Child No abnormalities are seen at birth or in early infancy Between the ages of 2 to 5 years the penis begins to enlarge and gradually develops to the size of the adult organ. At the same time pubic hair appears followed by general body hair growth and acne It is important to note that the growth of the penis the scrotum and the male body hair is not accompanied by testicular enlargement these glands remaining infantile in size

(*b*) *Somatic Effects of Androgen*

Increased somatic growth is evident from late infancy The muscle bulk is increased and of male type the female child has the general body contours of the adolescent boy and the male has been compared to an infant Hercules

Skeletal growth is accelerated in both sexes Girls develop broad shoulders and narrow hips Centres of ossification appear prematurely and long bone growth is excessively rapid the child becoming taller than his or her contemporaries However epiphyseal closure is even more rapid than the upward growth all epiphyses close by the age of 14 years so that growth is arrested Hence in late adolescence and adult life the patient is of abnormally short stature with relatively short limbs occasionally so short as to suggest achondroplasia

(*c*) *Adrenal Insufficiency*

Clinical evidence of adrenal failure in terms of gluco- and mineralo-

brother and sister may be affected The genesis of the condition appears to be an inborn error of adrenal metabolism by which the gland is incapable of normal synthesis of C21 steroids with metabolic activity As this part of hormone synthesis is dependent on adrenal enzymes the most likely genetic abnormality is the absence of an enzyme system The consequence of impaired hydrocortisone production is an alteration in the normal feed-back mechanism by which the level of circulating glucocorticoids determines pituitary activity allowing an excessive secretion of adrenocorticotrophin This causes bilateral adrenal hyperplasia and an excessive amount of C19 and C21 hormone precursors derived from cholesterol The C19 steroids are androgenic causing the early development of male characteristics in both sexes and a raised level of 17 ketosteroid excretion Soon after birth the child will either die from the deficiency of corticoids or the stimulus of A C T H will provide enough C21 precursors for some type of metabolically active hormone to be formed by an alternative pathway of synthesis In those who survive without clinical evidence of adrenal failure the essential biochemical lesion *can be demonstrated by the abnormal response to injected* A C T H It is apparent that gross virilization of the female and sexual precocity in the male are inevitable side effects of the attempt to produce sufficient corticosteroids to preserve life The condition should not be considered as a primary disorder of sex hormones but as an inborn error of metabolism in which the pituitary-adrenal mechanism is over-stimulated to compensate for adrenal insufficiency

CLINICAL PICTURE

This depends on the development of sex characteristics influenced by androgen the effects of androgen on somatic growth and insufficiency of other adrenal hormones

(a) Sex Effects

The Female Child The degree to which the genitalia are deformed towards a male pattern depends on the stage of embryonic life at which androgen secretion starts The majority of cases are affected between the 12th and 20th week of gestation with arrest of female development before the urogenital sinus is fully differentiated At birth the external genitalia simulate those of the male hence the term pseudohermaphrodite The clitoris is greatly enlarged and often mistaken for a penis a narrow vagina communicates with the urethra to form a cloaca More rarely with a later onset of virilization the vagina is larger although the urethra opens

the most useful diagnostic test as the normal 17 ketosteroid excretion of the child is almost nil

TREATMENT

Cortisone will raise the level of circulating glucocorticoids diminish the secretion of A C T H and suppress the excessive output of ad enal androgen. Thus the progressive virilization of the female hermaphrodite can be arrested and normal feminine development will take place In male patients cortisone will halt the progress of sexual precocity

For infants an oral dose of cortisone 12 5 mg to 25 mg daily (or 25 mg i m twice or thrice weekly) is an adequate dose but older children and adults require from 25 mg to 75 mg daily by mouth (or 100 mg i m twice or thrice weekly) Patients with Addisonian symptoms require a high salt diet in addition to cortisone A reduction of 17 ketosteroid excretion to normal levels is a good index of effective treatment.

The results of cortisone therapy are excellent provided the treatment is continued indefinitely There is no indication for adrenalectomy which is a dangerous operation in these patients who are so liable to death in Addisonian crisis

ACQUIRED ADRENAL VIRILISM

The adrenal cortex may produce excess androgens at any time of life This is an acquired lesion without evidence of insufficient production of other hormones As in Cushing s syndrome the anatomical lesion may be a tumour or bilateral adrenal hyperplasia.

Growth of facial hair and an increase in body hair especially of the pubic hair which extends upwards to the umbilicus is associated with a thinning of the scalp hair which can progress to frontal baldness The clitoris enlarges the voice deepens and oligomenorrhoea is followed by amenorrhoea If the patient is still immature the somatic growth effect of androgen is apparent from early fusing of the epiphyses and the masculine contour of the body In some patients plethora obesity and even hypertension suggest a mixed picture of virilism and Cushing s syndrome

A tumour may arise at any age the clinical manifestations being progressive and severe In children virilization not due to congenital adrenal hyperplasia is nearly always caused by a tumour However the majority of patients develop the syndrome towards the end of puberty or in early adult life without tumour formation At all ages the urinary excretion of 17 ketosteroids is raised although there is little correlation between the degree of virilism and the quantity of 17 ketosteroids excreted Virilizing

corticoids develops during the first eight weeks of life Failure to thrive persistent vomiting dehydration and collapse with peripheral vascular failure resemble the Addisonian crisis of the adult The lowered serum sodium and raised potassium of adrenocortical failure are found together with continued urinary loss of sodium chloride Frank hypoglycaemia is rare but has been described in association with episodes of unconscious ness sweating and cyanosis As in adult cases of adrenal failure sudden crisis is precipitated by infection or operative trauma and death may take place despite restoration of the electrolyte balance

The proportion of cases which exhibit frank adrenal failure is uncertain There appears to be a milder grade of the disease in which the effect of excessive androgen is not apparent until early childhood and symptoms of adrenal failure are absent However in some patients there is a past history of vomiting attacks which caused prostration or some trauma or infection induces these symptoms for the first time Addisonian pigmenta tion is found in many patients even without other evidence of adrenal failure Lastly administration of A C T H will elicit an abnormal response (no salt retention no potassium diuresis and no fall in the eosinophil count) in any case whether or not adrenal insufficiency has been demon strated

Diagnosis

In female infants the differential diagnosis is from the various forms of pseudohermaphroditism both male and female The anatomy of the genitalia may be visualized by radiography using contrast media A hysterogram reveals a uterus and fallopian tubes although the external genitalia may resemble the male The onset of vomiting dehydration and collapse in an infant with abnormal genitalia should suggest imme- diately the diagnosis of adrenal pseudohermaphroditism with adrenal failure

Diagnosis at a later stage when a young girl presents with signs of virilism lies between a functioning adrenal tumour and congenital adrenal hyperplasia Evidence in favour of the latter is markedly increased bone age (determined radiologically) the presence of a common cloaca for urethra and vagina or a family history of genital abnormality

Male patients present in infancy *with symptoms of adrenal failure in* the absence of genital abnormality In childhood the presentation is with premature development of secondary sex characters without testicular maturation to be differentiated from other causes of sexual precocity

In both cases the urinary excretion of 17 ketosteroids is raised providing

side to the tumour is not atrophic and continues to function normally In consequence there is no risk of post-operative adrenal insufficiency Even after removal of a tumour the hirsutes tends to persist which is a great disappointment to the patient In other cases unilateral adrenalectomy has been advocated but the final result is poor because the opposite adrenal hypertrophies and continues to secrete excessive androgen. A bilateral subtotal adrenalectomy is more successful but a hazardous operation for a patient whose health is not impaired however distressing her appearance In some instances cortisone therapy is as effective as in congenital adrenal hyperplasia with excess androgen production. It is always worthwhile determining the effect of cortisone on the 17 ketosteroid output and continuing the administration of cortisone if the 17 ketosteroid excretion is diminished

For the multitude of hirsute women without evidence of virilization endocrinology offers no real hope Oestrogens are remarkably ineffective on hair growth although acne may disappear with their use Cosmetic methods of depilation should always be employed electrolysis although time-consuming and painful gives the best chance of permanent removal of face hair Incidentally the practice of shaving body or limb hair is not to be despised for there is no evidence that this increases the rate of hair growth.

Excessive Oestrogen Production

The adrenal cortex secretes some oestrogen when functioning normally It is of interest that oestrogen may be secreted in excess in the presence of extreme virilism but this makes no alteration in the clinical picture as the amount of adrenal androgen is so great

A few cases of adrenal tumours with a predominant secretion of oestrogen have been described in boys and men. Atrophy of the testes loss of face hair and considerable development of the breasts form the clinical picture

Primary Aldosteronism

Very recently it has been recognized that an adrenal tumour can secrete aldosterone in great excess this hormone being the most potent mineralocorticoid Severe potassium deficiency results the patient presenting with extreme weakness or even paralysis of the muscles Sodium retention is not marked but hypertension is usually a feature of the disturbance The serum potassium is extremely low although urinary excretion continues Attempts to correct the potassium deficiency by the administra-

tumours are associated with a high level of dehydro-iso-androsterone excretion (a β-ketosteroid on digitonin precipitation) which is not present if the adrenals are hyperplastic

Diagnosis

There is no problem in recognizing the fully developed syndrome in which the differentiation between tumour and hyperplasia must be made by radiography and steroid excretion studies Total ketosteroid excretion of over 100 mg daily is strongly in favour of a tumour without recourse to the measurement of dehydro-iso-androsterone output

It is the minor grades of apparent masculinization that provide the problem mainly because the patient is so distressed by her appearance that she cannot believe that endocrinology will not provide a magic answer Idiopathic hirsutes involving the face and the body is a particularly distressing condition The hair growth is widespread and not localized to the sex hair of the body nor is it associated with thinning of the scalp hair indeed the scalp hair often grows luxuriantly Familial and racial factors play a large part in the aetiology and there is no suggestion of an endocrine disturbance In fact many such women conceive and bear children normally

Another large group of patients develop some male type body hair often with acne but have no menstrual disturbance or enlargement of the clitoris Their body contours are neuter or male-like rather than female the condition arises during puberty but is not progressive (the 17 ketosteroid output is just above the upper limit of normality) Such patients suffer from a constitutional variation rather than an acquired disease of adrenal function

Temporary virilization during puberty or the menopause may be of adrenal origin but does not progress as the initial physiological disturbance disappears Such a condition is easily confused with progressive virilism but the prospect of natural arrest of the disturbance should curb the physician s enthusiasm for radical treatment

Finally excessive androgen production by the ovary usually from a virilizing tumour mimics the clinical signs of adrenal virilism A minor increase in 17 ketosteroids with marked evidence of virilism is suggestive of an ovarian tumour The point cannot be settled unless every case of virilism has a thorough pelvic examination preferably under anaesthesia

Treatment

The only satisfactory form of treatment is removal of a virilizing tumour In contrast to Cushing s syndrome the adrenal on the opposite

CHAPTER VI

THE PARATHYROIDS

Anatomy and Physiology

The parathyroid glands usually four in number are embedded in the connective tissue of the posterolateral aspect of the thyroid. Each gland is ovoid in shape weighing from 20-50 mg but the size and even the number of glands is variable and often parathyroid tissue is found in the mediastinum. The gland is composed of loosely arranged masses of polyhedral cells Two cells are recognized the chief cell with a large nucleus and poorly staining cytoplasm devoid of granules and the oxyphil cell with many eosinophilic granules in the cytoplasm. It is probable that the hormone is elaborated by the chief cells

Parathyroid hormone is protein in nature but has not yet been prepared in pure form The rate of hormone release does not appear to be under pituitary control, but is governed by the level of circulating calcium. A fall in plasma calcium concentration increases hormone secretion, which is diminished by a rise in calcium

The hormone plays an important role in the maintenance of normal calcium and phosphorus levels in blood and bone and parathyroid activity is affected by any disease which alters the normal equilibrium of these elements

Extirpation of the parathyroids results in a sharp fall in serum calcium and a rise in phosphorus These changes are reversed by the administration of parathyroid hormone which, if given in excessive dosage causes a rise in calcium above the normal serum concentration and a concomitant fall in phosphorus

The site of action for the hormone has been debated extensively Some have claimed that its effect is primarily on the kidney inhibiting phosphorus re-absorption by the tubules and that all other effects follow upon the resulting phosphate diuresis Others consider that the hormone primarily affects bone causing an increase in osteoclastic activity so that calcium and phosphorus are released from bone into the circulation. It is probable that both schools of thought are correct and that the hormone has two separate sites of primary action, the osteoclasts and the renal tubules

tion of potassium appear to fail because the urinary excretion of potassium is so great Renal impairment is the rule and these cases have probably been labelled potassium-losing nephritis in the past At the present moment the exact clinical differentiation of primary aldosteronism from a primary renal lesion with potassium loss is obscure It should be remembered that potassium deficiency due to hydrocortisone excess is found in Cushing s syndrome *In primary renal disease potassium deficiency is* associated with acidosis but in primary aldosteronism alkalosis occurs

shortly as carpopedal spasm More distressing is generalized tetany in which the whole body musculature is seized by tonic spasm in a convulsion often mistaken for epilepsy A dangerous aspect of this which may also occur as a solitary manifestation is laryngeal spasm leading to asphyxia

A tetanic state may be latent without spontaneous manifestations Under these conditions frank tetany can be elicited by various manœuvres Voluntary overbreathing will often induce sufficient alkalosis to produce tetany Constriction of the circulation by inflating a sphygmomanometer cuff on the arm up to above systolic blood pressure will produce carpopedal spasm within three minutes if latent tetany is present (Trousseau s sign) A more delicate test is the production of muscular twitching in the face (particularly of the upper lip) by tapping over the facial nerve just below and in front of the ear (Chvostek s sign)

Hypoparathyroidism

A primary disturbance of function arises either from destructive lesions of the glands or their removal by operation. Secondary dysfunction due to some other disorder involving calcium metabolism may occur Lastly normal parathyroid function can be associated with failure of the body to respond to the hormone as in the very rare cases of pseudo-hypoparathyroidism.

Spontaneous Hypoparathyroidism

This rare condition of uncertain aetiology develops during childhood in 70 per cent of cases Both sexes are equally affected The parathyroids may be absent from a congenital anatomic defect or perhaps destroyed by virus infection or haemorrhage into the glands

Clinical Picture

Tetany is present in all cases varying from painful cramps of the limbs to generalized convulsions The epileptiform nature of the latter commonly leads to misdiagnosis

A long-standing disturbance of serum calcium not only causes repeated convulsions but leads to some mental deficiency Electro-encephalographic abnormalities are very common, and in some cases papilloedema is seen Why this should occur is obscure but it is a misleading sign which suggests a primary intracranial lesion rather than hypoparathyroidism

Some stunting of growth is usual and the physique is poor A curious feature is the marked tendency to recurrent fungus infections of mouth and

TETANY

The essential clinical feature of parathyroid extirpation is tetany so that it is proper to discuss the mechanism which may give rise to this curious state of excessive neuromuscular excitability The most important feature in the production of tetany is a lowering of the ionized calcium concentration in the blood and extracellular fluid About 66 per cent of calcium in the blood is present in a diffusable ionized form the rest being loosely bound to protein in a non-diffusable state The amount of ionized calcium can be calculated when the total serum calcium and plasma protein are known Alkalosis prevents normal ionization of calcium leading to tetany in the presence of a normal total serum calcium or making latent tetany obvious if the calcium content of the blood is somewhat reduced High serum phosphate concentrations increase the severity of tetany and magnesium can play an obscure role in its pathogenesis The relation of tetany to various disturbances is illustrated in the accompanying table

TYPES OF TETANY

	Serum Concentrations			
Disease	Ca	P	CO_2	Cl
1 *Vit D Deficiency* (Rickets – Osteomalacia Steatorrhoea)	↓↔	↓↔	↔	↔
2 Alkalosis (Hysterical overbreathing vomiting)	↔	↔	↑	↓ (vomiting)
3 Renal Failure	↔↓	↑	↓	↔
4 Hypoparathyroidism	↓	↑	↔	↔

↔ Normal ↑ Increased ↓ Decreased

CLINICAL SIGNS OF TETANY

The excessive neuromuscular excitability is manifest by pain and paraesthesiae in the limbs together with twitching of muscle groups sometimes culminating in a generalized convulsion Distal limb muscles are most commonly affected An onset with fibrillary twitching rapidly gives way to a tonic spasm lasting from seconds to a few minutes The arm is held in flexion at elbow and wrist the thumb adducted to the palm the metacarpophalangeal joints flexed and the fingers straight This classical attitude of tetany is termed main d'accoucheur The lower limb is affected in a similar manner with the feet held in an equinovarus position Luckily the manifestations of tetany in the limbs can be described

probably of genetic origin and is always associated with certain developmental abnormalities The face is usually rounded and plump and the stature thickset and short The hands are remarkable for the short stubby fingers and short metacarpals Often the index finger is longer than the other fingers Soft tissue calcification is seen frequently and is remarkably widespread

Diagnosis

The first point is to establish the presence of tetany This is not difficult when classical carpopedal spasm is observed but generalized tetanic convulsions are commonly mistaken for epilepsy Indeed many cases of idiopathic hypoparathyroidism have been treated as epileptics for long periods However observation of ectodermal abnormalities and the presence of cataracts should lead to the demonstration of latent tetany and the correct diagnosis The presence of latent tetany is established by eliciting a positive Trousseau s or Chvostek s sign and the precipitation of carpopedal spasm by voluntary overbreathing

The essential biochemical finding is a low serum calcium (7 5 to 4 0 mg per cent) and a raised serum inorganic phosphorus (4 5 to 6 5 mg per cent in adults 6 0 to 10 mg per cent in children) The serum alkaline phosphatase is normal Rickets in a child is distinguished by the presence of active bone disease (evident on X-ray) a high alkaline phosphatase and no significant rise in serum phosphorus At all ages steatorrhoea must be considered as a cause of tetany but if associated with osteomalacia there is little question of hypoparathyroidism On the other hand absence of bone disease when the serum calcium is low suggests a degree of secondary hypoparathyroidism the demonstration of steatorrhoea excluding primary failure of the glands A low serum calcium with high phosphorus and tetany is found in chronic renal failure but the evidence for renal impairment reveals the correct diagnosis

Tetany after thyroid operations is never a problem in diagnosis it is wise to measure the serum calcium in any patient who complains of cramp after thyroidectomy The rare entity of pseudo-hypoparathyroidism is diagnosed on the physical habitus and the failure to respond to injected parathyroid hormone (see Appendix for technique of Ellsworth-Howard Test)

Treatment

The emergency treatment of severe tetany is the intravenous injection of 10 cc of calcium gluconate (10 per cent solution) The injection must

throat usually from *candida albicans* Other ectodermal abnormalities include delayed poor dentition dry scaly skin and slowly growing brittle nails The low serum calcium results in metastatic calcification which involves the basal ganglia and the lens of the eye. X-ray examination reveals the former which is symptomless but the latter may blind the patient with calcium deposition in the crystalline lens In the early stages lenticular calcification must be sought with the slip lamp but later bilateral cataracts are very obvious The lens changes are not specific to hypoparathyroidism but are found in any condition (e g steatorrhoea) associated with a very low serum calcium

POST-OPERATIVE HYPOPARATHYROIDISM

This occurs after subtotal thyroidectomy or after removal of a functioning parathyroid tumour In both instances the resulting tetany is usually transient and does not persist beyond the initial post-operative period The patient complains of cramps and tingling in the hands carpopedal spasm is the most obvious clinical feature Under these conditions the parathyroids recover from operative trauma but occasionally all parathyroid tissue is removed during thyroidectomy leading to permanent tetany As compared to the spontaneous disease generalized convulsions are a rare occurrence Ectodermal abnormalities are rare although cataracts appear if the low serum calcium persists for a long time

SECONDARY HYPOPARATHYROIDISM

This condition is of physiological rather than practical interest because it illustrates the role of the parathyroids in non-endocrine disease In *steatorrhoea calcium* is absorbed poorly resulting in a negative calcium balance In consequence the serum calcium tends to drop but the fall is arrested by *increased parathyroid activity* Failure *of this compensatory mechanism* or secondary hypoparathyroidism results in a low serum calcium with raised serum *phosphorus concentration It is of interest* that such cases do not exhibit gross osteomalacia

PSEUDO-HYPOPARATHYROIDISM

Once again the rarity of this curious disorder makes it unimportant clinically but of great interest physiologically The symptomatology and biochemical findings are similar to those for true hypoparathyroidism but normal parathyroid glands are present and there is no response to injected parathyroid hormone In short the disease is not due to a lack of hormone but to a failure of the body to respond to it. The disturbance is

probably of genetic origin and is always associated with certain developmental abnormalities The face is usually rounded and plump and the stature thickset and short The hands are remarkable for the short stubby fingers and short metacarpals Often the index finger is longer than the other fingers Soft tissue calcification is seen frequently and is remarkably widespread

DIAGNOSIS

The first point is to establish the presence of tetany This is not difficult when classical carpopedal spasm is observed but generalized tetanic convulsions are commonly mistaken for epilepsy Indeed many cases of idiopathic hypoparathyroidism have been treated as epileptics for long periods However observation of ectodermal abnormalities and the presence of cataracts should lead to the demonstration of latent tetany and the correct diagnosis The presence of latent tetany is established by eliciting a positive Trousseau s or Chvostek s sign and the precipitation of carpopedal spasm by voluntary overbreathing

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TREATMENT

The emergency treatment of severe tetany is the intravenous injection of 10 cc of calcium gluconate (10 per cent solution) The injection must

be given slowly to avoid any likelihood of affecting the heart Occasionally removal of a parathyroid tumour is followed by such severe and persistent tetany that a continuous intravenous drip of calcium gluconate is required (100 cc of 10 per cent calcium gluconate added to 1000 cc of 5 per cent dextrose solution)

The therapeutic role of parathyroid hormone is extremely limited despite the logic of its use In a short time the body fails to respond to its injection because some antibody reaction is set up It is doubtful whether a true antihormone is formed, more probably there is antibody formation to the impurities of the preparation However intramuscular administration in a dose of 50-100 units twice daily for a few days only may tide over an acute phase of tetany until long term treatment can be established

Long term treatment consists of a dietary regime and the administration of calciferol *It is obvious that the intake of calcium must be high but the importance of a high calcium to phosphorus ratio is commonly neglected* Thus milk (or cheese) is a rich source of calcium but its high phosphorus content makes it utterly unsuitable in the treatment of hypoparathyroidism A considerable improvement in the serum calcium level with a concomitant fall in phosphorus can be obtained by a strict low phosphorus high calcium diet However this is very dull and unpalatable so that *no patient will remain on the regime An adequate compromise is a diet that* excludes milk and cheese but is otherwise normal Additional calcium is required as tablets of calcium gluconate (8-16 grams daily) Calcium chloride has been advocated as its acidifying effect promotes calcium absorption and diminishes tetany by creating mild acidosis However the acidosis may be harmful and there is no advantage in the use of the chloride when calciferol is also given

Calciferol (Vitamin D_2) has a powerful effect on the absorption of calcium and also causes an increase in renal loss of phosphorus In this latter action it can replace parathyroid hormone Another product of irradiated ergosterol which mimics the action of the hormone is dihydrotachysterol (A T 10) *The cost of this substance is so much more than* calciferol that there is no reason to use it as a routine in long term therapy However there are instances of calciferol resistance arising during treatment When this occurs a transfer of therapy to A T 10 will be effective

Calciferol is more active in the presence of parathyroid hormone with the consequence that high dosage is required in hypoparthyroidism Its action is prolonged which leads to difficulty in regulating the dose and necessitates the immediate cessation of treatment if the serum calcium concentration reaches abnormally high levels An initial dose of 1 mg

(40 000 units) daily is not excessive the final maintenance dose varies from 1 to 10 mg The dose of A T 10 is similar to that for calciferol Rising requirements of calciferol should be met by changing the therapy to A T 10 at a dose equivalent to the original effective dose of calciferol

Hyperparathyroidism

Excessive production of parathyroid hormone may result from primary disease of the gland or as a secondary response to certain disturbances of calcium metabolism

Primary Hyperparathyroidism

PATHOLOGY

By far the most common cause of this condition is a parathyroid adenoma The tumour is usually small and seldom palpable An important point is that 10 per cent of these adenomata are found not in the neck but in the mediastinum Occasionally generalized parathyroid hyperplasia causes primary hyperparathyroidism This histological diagnosis is always suspect as it is so difficult to differentiate from secondary parathyroid hypertrophy The rare malignant parathyroid tumours are very seldom associated with disturbed function

The exact significance of the biochemical abnormalities is still debatable The argument revolves round the primary site of action of parathyroid hormone It has already been stated that there are probably two primary sites of action namely the osteoclasts and the renal tubules However hyperparathyroidism can be present as a renal disturbance without any demonstrable bone disease Exponents of the renal theory point to the fact that this type of the disease can be present for many years and does not represent an early phase On the other hand when bone disease is present the osteoclasts are so stimulated as to form tumours The two views may be reconciled on the supposition that patients show a variable sensitivity of bone and kidney to hormone stimulation

Leaving aside theories the biochemical changes themselves are clear Renal tubular reabsorption of phosphorus is diminished and the serum phosphorus falls In relation to the serum phosphate fall and probably from direct stimulation of osteoclasts both calcium and phosphate leave bone As there is no abnormal renal handling of calcium the serum calcium rises With this rise increasing quantities of calcium pass into the urine In consequence the patient is liable to develop calcium phosphate calculi in both kidneys As osteoclastic activity increases the serum alkaline phosphatase rises and further bone activity leads to the formation of osteoclastomata

be given slowly to avoid any likelihood of affecting the heart Occasionally removal of a parathyroid tumour is followed by such severe and persistent tetany that a continuous intravenous drip of calcium gluconate is required (100 cc of 10 per cent calcium gluconate added to 1000 cc of 5 per cent dextrose solution)

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The renal calculi present with colic or recurrent urinary infection. They are found in both kidneys and reoccur after removal Therefore any patient who has a long history of bilateral recurrent calcium phosphate calculi should be considered as a possible case of hyperparathyroidism

Renal function is impaired to a degree dependent on the amount of infection that has occurred and the amount of nephrocalcinosis Considerable recovery of function is not uncommon after successful removal of a parathyroid adenoma but in cases with gross renal impairment operation is of no avail and renal failure progresses to fatal uraemia

The characteristic low serum phosphorus is not found in the presence of renal failure Indeed phosphate retention is likely to accompany the urea retention This complicates the diagnostic value of serum chemistry

In the slow evolution of the disease the functional state of the kidneys rather than the bone dominates the picture and uraemia is the most common cause of death

DIAGNOSIS

The patient may present with or without bone disease In both types the history may reveal recurrent gastro-intestinal disturbance of thirst and polyuria suggestive of hypercalcuria If the patient presents with symptoms of renal calculi the nature of the calculus and X-ray evidence of nephrocalcinosis will aid the diagnosis At all times X-ray examination of the bones is necessary to determine the degree of osteoporosis and more particularly the presence of spontaneous fractures or cystic areas subperiosteal resorption of bone is also seen In the absence of localizing bone symptoms X-ray of the skull hand and femora are required

It is obvious that the serum calcium phosphorus and alkaline phosphatase must be measured The usual range of calcium concentration is 12-18 mg per cent but the value may be normal The phasic nature of hypercalcaemia makes it important to perform serial calcium determinations if the first reading is normal Serum phosphorus is lowered (below 2 5 mg per cent) unless there is impaired renal function Therefore interpretation of the phosphorus concentration is made in the light of renal function tests Alkaline phosphatase is raised only in the presence of bone disease

There is unfortunately no specific test for parathyroid hormone At the present time the most important aid to the investigations already listed is a measurement of urinary calcium output when the patient has been maintained on a low calcium (below 120 mg daily) diet for at least five days A 24-hour urinary calcium output which is repeatedly over 250 mg strongly suggests hyperparathyroidism.

Clinical Picture

Both sexes are affected equally, and at any age The diagnosis is most common in middle-age but the great length of the natural history prior to recognition of the condition in many cases makes it difficult to give a true estimate of the age of onset

The symptoms and signs can be classified on a physiological basis It will be seen that the condition can be divided broadly into cases presenting as recurrent renal calculi and those presenting with bone disease The renal type is more common than the bony disease and many patients have suffered for years from recurrent renal calculi probably entailing several operations before the correct diagnosis has been made

(a) *Symptoms of Hypercalcaemia*

The degree to which the serum calcium is raised is as variable as the periodicity of hypercalcaemia In consequence the symptoms are variable in intensity and time A high serum calcium causes gastro-intestinal disturbance with episodes of anorexia vomiting and sometimes diarrhoea which last from days to weeks The excessive urinary exretion of calcium is accompanied by polyuria and thirst Lastly muscular weakness and diffuse pain in the limbs add to the general discomfort of the patient

(b) *Bony Changes*

Excessive stimulation of osteoclastic activity by parathyroid hormone leads to general demineralization of bone Unlike osteoporosis the process involves the skull which presents a uniform granular mottled appearance on X-ray The weakened bones are liable to spontaneous fracture but such fractures heal with normal callus Finally growth of the osteoclastic cells forms tumours which have a predilection for the jaw metacarpals metatarsals and the ends of long bones On X-ray the appearance is of cystic change and indeed such changes are present in some of the tumours With advanced bone changes there is considerable fibrosis of the marrow which results in anaemia and leucopenia. Pathologically the disease is well named generalized osteitis fibrosa cystica Clinically it causes severe bone pain and spontaneous fractures The bones break rather than bend in contrast to osteomalacia

(c) *Renal Changes*

These are of great importance because more cases of hyperparathyroidism suffer from renal calculi than bone disease The majority of the calculi consist of calcium phosphate Calcium deposition also occurs throughout the substance of the kidney and may be present in the absence of calculi Similar metastatic calcification may also occur in the muscles and lungs

tion of the one tumour for cases have been reported with two adenomata If no tumour is found in the neck exploration of the anterior and posterior mediastinum is necessary because parathyroid adenomata can occur in these sites

The post-operative disturbance of calcium metabolism will be in proportion to the severity of the bone disease A severely demineralized skeleton will absorb great quantities of calcium directly the excess of parathyroid hormone is removed Consequently a profound drop in serum calcium with prolonged tetany will occur This event should be anticipated and prevented by the administration of a very high calcium intake prior to operation and a continuous intravenous infusion of calcium gluconate in 5 per cent dextrose from the moment of operation (100 c c of 10 per cent calcium gluconate to 1000 c c. dextrose solution) Therapy is regulated by repeated serum calcium determinations and a clinical watch for the appearance of tetany For some obscure reason oliguria may complicate the immediate post-operative course so that measurement of urinary output is necessary to gauge the correct fluid intake

SECONDARY HYPERPARATHYROIDISM

Parathyroid activity is increased in conditions which lower the serum calcium namely rickets osteomalacia prolonged lactation and chronic renal failure

Enlarged parathyroid glands are a frequent autopsy finding in chronic renal disease with death in uraemia but it is not certain that this indicates increased function It has been suggested that renal failure decreases the serum calcium either by excessive urinary excretion in an attempt to overcome acidosis (when the kidney can no longer form ammonia) or by failure to secrete phosphate leading to a raised serum phosphorus A low serum calcium and bicarbonate with raised serum phosphorus may or may not be associated with bony lesions A bewildering variety of bone disease can occur from osteosclerosis to cyst formation but the more common picture is that of osteomalacia or osteitis fibrosa, sometimes with metastatic calcification in muscles or lungs The association of bony disease and chronic renal failure is distinct from primary hyperthyroidism in that the serum calcium is not raised the kidney is not calcified and the plasma bicarbonate is lowered

The differential diagnosis lies with the following diseases

Secondary Hyperparathyroidism

(See appropriate section (page 123) for discussion.)

Recurrent Renal Calculi of Other Types

The nature of the calculus the absence of bone lesions and the normal serum chemistry and a low calcium excretion on a low calcium diet will distinguish this group In practice it is more common to forget the occurrence of hyperparathyroidism in the guise of renal calculi

Osteoporosis

A normal X-ray of skull an absence of cyst formation in bone together with normal serum chemistry and a normal renal tract differentiate this condition from parathyroid disease There are rare instances of acute osteoporosis with hypercalcaemia occurring in young patients who are immobilized after severe bony injury Similar episodes may complicate the fracture of a bone affected by Paget s disease

Osteomalacia

Secondary hyperparathyroidism is associated with this disease and therefore it is discussed in the appropriate section (page 123)

Multiple Myelomatosis

Bone pains anaemia renal impairment and sometimes a raised serum calcium suggest parathyroid disease The absence of renal calculi or calcification the presence of a high sedimentation rate and reversed albumin/globulin ratio indicate the correct diagnosis which is confirmed by the finding of myeloma cells on sternal puncture

Rare Causes of Confusion

Localized giant cell tumours of bone are similar on X-ray to the tumours of hyperparathyroidism but there is no evidence of generalized disturbance Occasionally Paget s disease may be superficially confusing in diagnosis, and also that rare entity of childhood polyostotic fibrous dysplasia Lastly intense polyuria associated with hypercalcaemia may suggest that the patient with a parathyroid adenoma has diabetes insipidus

Treatment

The only bar to removal of a parathyroid adenoma is gross chronic renal failure which is judged to be irreversible Apart from this the *correct treatment* is surgical exploration of the neck to find and remove the offending tumour The surgeon must not be content with the identifica-

ing of insulin following a meal. It occurs in highly strung and neurotic individuals who possess vasomotor instability and gastric hyperacidity The same disorder is probably responsible for hypoglycaemia in patients who have had a gastrectomy The rapid absorption of carbohydrate after this operation may play some part by causing a transient initial hyperglycaemia. The extreme sensitivity of the pancreas is probably related to an unstable autonomic system with vagal overaction

The symptoms of hypoglycaemia are seldom severe in the alimentary and functional cases Characteristically the onset of symptoms follows a meal particularly if it contains a large proportion of carbohydrate Dizziness faintness sweating and trembling are the usual complaints but coma does not occur and the syndrome does not progress in severity The diagnosis lies in the clinical interpretation of the symptoms and the proof that they are related to a lowered blood-sugar (usually about 50–65 mg per cent) Symptoms are not produced by prolonged fasting and the oral sugar tolerance test shows a normal fasting blood sugar with a later drop to hypoglycaemia As carbohydrate exaggerates the symptoms treatment consists of a high protein and low carbohydrate diet taken in frequent small meals The patient should avoid all sugar in his diet Of course sugar will relieve the symptoms if they occur but prevention of symptoms can be achieved only by cutting out sugar from the diet

Tumours of the Islets of Langerhans

Functioning tumours of the islets of Langerhans (Insulinomas) may arise at any age the peak incidence lying between 40–50 years Both sexes are equally affected The benign adenoma is the most common growth outnumbering the malignant tumours with hepatic metastases by ten to one It is important to realize that in about 10 per cent of cases more than one adenoma is present in the pancreas The tumour may be found in any part of the pancreas there is no truth in the suggestion that they are more frequently found in the tail. However tumours in the head of the pancreas are less accessible to the surgeon than those in the tail

Occasionally the pancreas is filled by hyperplastic islets of Langerhans or even a diffuse adenomatosis Such a pathology is more common in children with hypoglycaemia but it is apparent from autopsy studies that hyperplastic islets of Langerhans are not necessarily associated with an increased secretion of insulin Indeed even modern staining methods for the β cells of the islets do not give a good correlation between histological appearance and functional capacity

CHAPTER VII

SPONTANEOUS HYPOGLYCAEMIA

SPONTANEOUS hypoglycaemia arises either from an excessive secretion of insulin from the islet cells of the pancreas or from a diminished secretion of insulin antagonists provided by the pituitary and the adrenal cortex The anterior pituitary antagonizes the hypoglycaemic effect of insulin by the secretion of growth hormone and by the secretion of A C T H The latter stimulates the adrenal cortex to secrete hydrocortisone which inhibits the action of insulin as well as promoting gluconeogenesis The types of spontaneous hypoglycaemia can be classified according to the primary disorder of function and the underlying anatomical lesion

CAUSES OF SPONTANEOUS HYPOGLYCAEMIA

A With no anatomical lesion
Functional (? autonomic imbalance)
Alimentary (post-gastrectomy)

B With anatomical lesion

1 Excessive insulin secretion
Adenoma of islet cells of pancreas
Carcinoma of islet cells of pancreas
Diffuse hyperplasia of islet cells of pancreas

2 Hypersensitivity to normal secretion of insulin
Primary adrenocortical failure
Primary anterior pituitary failure

3 Disturbance of glycogen storage
Glycogen storage disease (Von Gierke s)
Cirrhosis of liver or acute yellow atrophy of liver

The clinically important conditions are the first three Hypoglycaemia *is only part of the picture of anterior pituitary or adrenocortical failure* and there is little likelihood of missing the relevant physical signs and symptoms of these conditions even if the immediate presenting symptom is due to a lowered blood-sugar Liver disease is very seldom associated with significant hypoglycaemia

Functional hypoglycaemia is due to a temporarily excessive outpour-

An accurate history is the most valuable diagnostic aid the probability of hypoglycaemia being tested by estimating the blood-sugar during a spontaneous attack or when an attack has been induced by fasting the patient for up to 24 hours Between attacks the patient exhibits no abnormal physical signs Obesity might be expected from hyperinsulinism but in fact is seldom seen

An erroneous diagnosis of hysteria or epilepsy is often made merely because the possibility of hypoglycaemia is overlooked When the stage of coma is reached the generalized rigidity of the patient with extensor plantar responses may suggest encephalitis or a mid brain tumour In the terminal phase confirmation of the correct diagnosis can be impossible because the blood sugar may be at a normal level despite continued unconsciousness Other forms of hypoglycaemia are not difficult to distinguish either by their characteristic relationship to meals without symptoms on fasting or by associated evidence of adrenal or hepatic failure Insulin or glucose tolerance tests have no consistent pattern in the presence of an insulinoma and are therefore valueless in diagnosis The distinction between a malignant and a benign islet cell tumour may be inferred from the rapid progression of symptoms which is more characteristic of the malignant growth or the palpation of an enlarged liver studded with metastases

TREATMENT

Surgical removal of the tumour is essential directly the diagnosis is established The operation may be dramatically successful even if the patient has been comatose for three or four days and exhibits decerebrate rigidity However such prolonged hypoglycaemia is likely to have caused irreversible damage to the brain, leading to intellectual impairment

On occasion the presence of a tumour may be in doubt despite clinical evidence of severe hypoglycaemia An exploratory laparotomy should be undertaken with a partial resection of the pancreas if no tumour can be found This situation usually arises in children their illness being successfully terminated by subtotal pancreatectomy despite the absence of demonstrable islet cell tumour or hyperplasia

Prior to operation it is not difficult to maintain a normal blood-sugar concentration by the infusion of glucose After operation transient hyperglycaemia is common but does not require insulin therapy The maintenance of the blood sugar in the presence of functioning metastases is a serious problem. Malignant islet cell tumours are seldom fatal from their invasive properties but kill by hypoglycaemia which cannot be

Clinical Picture

The symptoms and signs of hypoglycaemia are widely known because of the large number of diabetics whose treatment with insulin makes them liable to such episodes It is a matter of speculation as to why the identical symptoms produced by an islet cell tumour are so seldom interpreted correctly The fact that a case of hyperinsulinism has been diagnosed by a nursing orderly because he was familiar with insulin shock therapy illustrates that awareness of the condition is the first step to recognition

There is an extraordinary variability in the time taken for the full development of the syndrome Some patients are deeply unconscious within two weeks of the first symptom while others suffer occasional mild attacks over many years before the tempo of the disease quickens and the diagnosis is made The usual course is one of progression not only in frequency of attacks but also in severity of the symptoms Characteristically the symptoms appear before breakfast and later on fasting or exertion

The symptoms are as variable as those induced by the injection of insulin Early manifestations include noisy drunken' behaviour with slurring of speech To the onlooker peculiar behaviour is obvious the housewife staggers from her bed to put the tea leaves in the marmalade and pour *boiling water over the cereal By the time she has eaten breakfast* her behaviour is normal and she has little recollection of her apparent stupidity Apart from a lightheadedness or a trance-like feeling the patient experiences blurring of vision or diplopia tingling around the mouth and intense sweating

As the attacks become more frequent and more severe stupor and transient coma are dominant signs Loss of consciousness is often accompanied by epileptiform convulsions with incontinence of urine Spontaneous recovery of consciousness is usual the patient having no memory of the attack and sometimes waking with a hemiparesis that disappears in a few hours Episodes of coma become prolonged until the terminal *attack which leaves the patient in a state of decerebrate rigidity lasting* days before death

Diagnosis

The cardinal points of diagnosis are the occurrence of attacks in a fasting state with blood-sugar values below 50 mg per cent and rapid clinical relief from the administration of glucose The episodic and variable nature of the illness is sometimes confusing the degree of hypoglycaemia is not constant symptoms being related to the speed of fall of blood sugar as much as the absolute degree of hypoglycaemia

CHAPTER VIII

THE GONADS

Heterosexual Development

The human embryo is essentially ambisexual up to the 25 m m stage After this the gonad differentiates into ovary or testis and the genital ducts develop according to the sex of the gonad the genital tract arises from the Wolfian duct in the male and from the Mullerian duct in the female The conditions controlling this development are not fully understood. The genetic sex is determined at fertilization, but later embryonic development may be influenced by genetic considerations and by hormonal or other organizing factors elaborated by the embryo or the mother If the embryonic gonad is removed or remains undifferentiated the sex development of the organism proceeds along feminine lines regardless of the genetic sex The secretion of androgen by the foetal adrenal will accentuate male characteristics despite a normal ovary as shown by the female pseudohermaphroditism of congenital adrenal virilism However the degree of hormonal control in normal sex development is uncertain.

The obscurity of this subject does not prevent a clinical approach which is based on physiological criteria The points to be considered are the genetic sex the gonad and its degree of development the external genitalia and the presence or absence of sex hormone activity Heterosexual development originates in the embryo or is acquired after birth acquired masculinization of the hitherto normal female or feminization of the male is always an endocrine disturbance with excessive hormone production of adrenal or gonad Embryonic abnormalities form the basis of hermaphroditism which may have a genetic or an endocrine basis Complete agenesis of the gonad, regardless of genetic sex is associated with feminine development which presents clinically as female sexual infantilism rather than as a problem of intersexuality The following classification will clarify these points

HETEROSEXUAL DEVELOPMENT PRESENT AT BIRTH

Gonadal Agenesis

This syndrome does not present a clinical problem of intersex Therefore it is discussed in a later section (page 133)

treated surgically The use of alloxan has proved disappointing and dangerous Administration of very large amounts of carbohydrate is seldom successful for any length of time The most promising form of therapy is cortisone which promotes gluconeogenesis and inhibits the action of insulin Obviously one is fighting a losing battle with a malignant tumour but cortisone may so moderate the attacks of hypoglycaemia that the patient s life is extended for several months

though menstruation is obviously absent because there is no uterus the body contours become essentially feminine with fully formed breasts The external genitalia appear feminine but the vagina is short It appears that the testes in these cases secrete oestrogen rather than androgen In one group of these cases there is a familial incidence of the syndrome and a complete absence of body hair (from end-organ insensitivity not lack of hormonal stimulus)

DIAGNOSIS

The diagnostic problems of intersexuality or hermaphroditism vary with the age of the patient Determining the sex of the new born child may be impossible on inspection of the genitalia and special investigation may be unwarranted at that stage In practice genital abnormalities often escape notice in the neonatal period and the mother does not seek medical advice for her child until he or she is several years old Lastly there are a group of patients who do not come to the doctor until they fail to mature normally at puberty Diagnosis on purely clinical grounds becomes easier with increasing age of the patient because the genital abnormality will have developed to its full extent It is useful to remember that true hermaphrodites are excessively rare and that in pseudohermaphrodites the female type is usually an example of congenital adrenal virilism and the male type of genetic origin Therefore the association of precocious secondary sex development and somatic growth with genital abnormality indicates a female pseudohermaphrodite but genital abnormality not associated with these features indicates a male pseudohermaphrodite

The special investigations required to confirm the diagnosis of congenital adrenal virilism have been detailed in a previous section (page 108) In cases with no hormonal abnormality the gonadal sex can be inferred by determining the chromosomal sex of the skin or leucocytes using special chromatin stains Apart from this the only sure method of complete diagnosis is exploratory laparotomy Such an operation cannot be justified by academic curiosity but is reasonable if surgical treatment is anticipated Congenital adrenal virilism can always be diagnosed without laparotomy moreover the risk of any operative procedure is increased in these cases

TREATMENT

Genetic and gonadal sex are not so important in therapy as the sex which the patient has adopted and the configuration of body and external

Gonads Differentiated

(a) *True Hermaphrodites*

Both ovary and testis present Genitalia of both sexes present internally and externally Outward appearance of genitalia may be predominantly male or female Secondary sex characters develop if at all at normal age, and mimic either sex

(b) *Pseudohermaphrodites*

(1) Female

Gonadal and genetic sex female External genitalia masculine but no testes or proper scrotum Uterus and fallopian tubes present if due to congenital adrenal virilism Secondary sex characters of male type are precocious in appearance if caused by adrenal androgens but may not appear in rare cases of genetic origin

(2) Male

Gonadal and genetic sex male External genitalia vary from essentially feminine to gross hypospadias of penis with cleft scrotum Secondary sex characters may be male or female often poorly developed but usually approximating to apparent sex of external genitalia

True hermaphroditism is excessively rare and can only be diagnosed by laparotomy The gonads lie intra-abdominally or in the inguinal canal sometimes in association with a hernia A composite organ ovotestis is usually found but a separate ovary and testis may be discovered Spermatogenesis does not arise in the testis The body habitus is more frequently male than female but body hair is usually of female type although breast development is poor Menstruation through a penile urethra can occur

Pseudohermaphroditism is a more common condition the sex of the patient being designated by the gonadal sex while the appearance of the genitalia resembles the sex opposite to that of the gonad The great majority of female pseudohermaphrodites have congenital adrenal virilism It is rare to find one of genetic origin In contrast male pseudohermaphrodites are usually of genetic origin In many the penis with gross hypospadias suggests an enlarged clitoris a cleft scrotum resembling a vulva although there is no vaginal opening and the labia minora are absent Testes may be palpable in the cleft scrotum or the inguinal canal There is no secondary sex development until the normal age of puberty at which time the growth of body hair and enlargement of the penis give further semblance of male sexuality although the degree of development is not that of a normal male The more remarkable cases are those of apparently normal feminine development in the presence of testes Al-

sexuality but the fact should never be forgotten in dealing with patients who are often convinced that their sex must be changing and are greatly relieved to find that this is not so

Gonadal Agenesis

The finding of rudimentary gonads in girls of short stature with hypogonadism and a variety of congenital lesions was described as ovarian agenesis until the recent introduction of skin or leucocyte sexing The logical change of nomenclature to gonadal agenesis followed the discovery that about 80 per cent of these patients have male type nuclei in skin and leucocytes

Before describing further clinical features of the syndrome it is worth while defining the significance of cytological tests of sex. In males the cell nuclei do not contain the specific sex chromatin which is present in all females This applies not only to normal people but to pseudohermaphrodites according to their gonadal sex But it does not follow that one can equate female type nuclei with genetic femaleness or male type nuclei with genetic maleness The absence of sex chromatin from the cell nuclei of the majority of the patients with the syndrome under discussion does not change girl into boy It does however provide a useful confirmation of diagnosis with its attendant prognostic significance It is quite wrong to allow any implication of sex reversal to be known by patient or parent

The origin of the syndrome lies in a defective germ plasm as suggested by the rudimentary gonads usually only a vestigial streak, by the high titre of follicle stimulating hormone (in the adult) indicating an intact pituitary and the association of other congenital lesions The internal genitalia show hypoplastic fallopian tubes a small uterus with a normal but immature vagina The external genitalia are essentially feminine although they remain immature

In stature the patient is short but not dwarfed the growth rate being within the limits of normal epiphyseal closure is only slightly delayed The general appearance is of a thickset person with short limbs the most characteristic deformity curiously reminiscent of the Sphinx is a webbing of the neck which extends in a fibrous band from behind the ear to the tips of the shoulder In the absence of webbing the neck may be extremely short Other deformities which may be present include cubitus valgus (with an increased carrying angle of the arm) pes cavus syndactyly spina bifida and chondrodystrophy of the dorsal vertebrae The defective

genitalia The older the patient the more important it is to conserve the sex in which he or she has been brought up from birth Integration with society is usually very successful and the patient is confident in being a man with deformed genitalia or a woman with superfluous hair If gonadal sex is opposite to that of the patient s social sex this knowledge should be kept secret by the doctor for revelation to the patient may result in suicide

The treatment of congenital adrenal virilism has already been discussed However there are some patients who have been brought up as boys and are well settled in this sex *Under these circumstances it is quite wrong to* induce feminine development by suppressing adrenal androgen secretion with cortisone The genitalia may be left alone or plastic operations performed to construct a penile urethra

The treatment of male pseudohermaphroditism depends on the sex adopted by the patient the external genitalia and the endocrine activity of the testis There is no problem if the patient brought up as a girl has feminine contours normal female breasts and external genitalia Such patients present with primary amenorrhoea the diagnosis is of academic interest only and no treatment is required At the other end of the scale there is the patient brought up as a boy whose genitalia are deformed but male-like Plastic surgery is usually required to remodel the genitalia to conform with a more masculine shape and androgen therapy is indicated if the testis fails to produce a normal amount of androgen at puberty A more difficult problem is presented by the patient brought up as a girl whose testes produce excess androgen at puberty causing virilization of an apparent female Orchidectomy is required followed by the administration of oestrogens to stimulate feminine characteristics and offset the hormonal withdrawal of castration Clitoridectomy and construction of an artificial vagina are two further surgical procedures of obvious value Removal of the gonad in any patient is only required if its hormonal action is contrary to the accepted sex of the patient

The social and mental aspects of hermaphroditism are very important Usually the libido of the patient corresponds to their accepted sex This in sharp contrast to those unfortunate people who possessing a normal fully developed body believe that they belong to the opposite sex This is a malady of the mind and not related to organic sex change There does not appear to be any possible justification for mutilating normal bodies to pander to these abnormal minds

Despite popular newspaper reports the human being does not change sex This should be *apparent from the foregoing discussion on inter-*

Precocious Sex Development

There is a considerable individual variation in the age of onset of normal puberty and its subsequent progress Sexual maturation follows the pattern indicated in the table which represents the average

DEVELOPMENT OF SEXUAL CHARACTERS

Age	*Boys*	*Girls*
10—11 years	Some enlargement of testes and penis	Budding of breast Downy pubic hair
11—12 years	Prostatic activity Downy pubic hair	Growth of labia vagina and uterus More pubic hair
12—13 years	Coarse (adult) pubic hair	Breasts filling out nipples developing
13—14 years	Rapid growth of penis and testes Subareola breast tissue	Axillary hair Menarche (anovulatory cycle at first)
14—15 years	Axillary hair Face hair begins Voice starts deepening Male body contours	Female body contours Regular ovulation
15—16 years	Spermatogenesis	

In this country evidence of sexual development before the age of 10 years should be considered as premature Precocious sexual development may involve secondary sex characters without gonadal maturation or be associated with gonadal growth to the stage of gametogenesis The former type is termed pseudopuberty and the latter true precocious puberty

Sexual precocity of all types will alter the somatic growth of the child accelerating the rate of growth and ossification As a result the child is taller than his contemporaries but early closure of the epiphyses leads to eventual short stature with short limbs in comparison to the length of the body Adrenal androgens are more potent than oestrogens in their action on somatic growth

The aetiology of sexual precocity can be classified according to the origin of the endocrine stimulus as shown in the accompanying table

AETIOLOGY OF PRECOCIOUS PUBERTY

(A) *True Puberty*

(1) Constitutional

(2) Hypothalamic lesions

Pineal tumours (boys only)

Basal meningitis

Tuberose sclerosis

Polyostotic fibrous dysplasia (girls only)

stature is not due to any endocrine influence but is of genetic origin Generalized osteoporosis may be seen in adults perhaps due to continued lack of oestrogen Other congenital lesions include mental retardation deafness myopia and lesions of the vascular system particularly coarctation of the aorta

Throughout childhood the condition is recognizable only by the association of congenital defects After the age of puberty hypogonadism with amenorrhoea is apparent but some scanty pubic and axillary hair grows under the stimulus of adrenal androgen Stature remains short and is not significantly affected by hormone administration as epiphyseal closure is not appreciably delayed There are no clinical signs of hypopituitarism the urine contains large amounts of gonadotrophins and a normal amount of 17 ketosteroids Absolute sterility is of course inevitable

An apparently similar syndrome occurs very rarely in obvious males Short stature and the congenital abnormalities already described are found with bilateral cryptorchidism and male hypogonadism

Diagnosis

The syndrome must be considered in the differential diagnosis of both male and female hypogonadism The short stature with sexual infantilism is likely to be confused with pituitary infantilism However it differs from this form of hypopituitarism in the presence of multiple congenital defects a short stocky build compared to a proportionate delicate skeleton with actual dwarfism and the growth of some pubic hair An almost normal 17 ketosteroid output and a raised level of urinary F S H excretion make a clear distinction from hypopituitarism In the majority of girls with the syndrome the diagnosis is confirmed by the finding of male type nuclei in the skin leucocytes or cells scraped from the buccal mucosa By this means the diagnosis can be made prior to the age of puberty

Treatment

In girls at the time of puberty growth of sexual characters *should be* induced by giving stilboestrol 2-5 mg daily (or its equivalent) As development proceeds the oestrogen should be stopped for one week in every month to allow a withdrawal bleed After maturation has been achieved there is no point at all in continuing therapy just for the sake of artificial menstruation If mental deficiency forms part of the syndrome it is inadvisable to induce sexual maturity In boys testosterone propionate 25 mg i m. twice weekly is appropriate treatment which should be continued as for other cases of hypogonadism (described on page 145)

with mental impairment may complicate the behaviour pattern associated with sexual maturation

Organic cerebral disease causes true puberty in both sexes which are equally affected Curiously enough pinealomas cause precocious puberty only in boys Not all such tumours are associated with precocity and there is no evidence to suggest a direct endocrine influence of the pineal This organ is not an endocrine gland and precocity is due to the involvement of the hypothalamus by the growth

In these cases the sexual maturation is an incident in a serious usually fatal neurological disease The exception to this rule is the occurrence of sexual precocity in girls suffering from the rare bone disease polyostotic fibrous dysplasia Although the disorder of function can be located in the hypothalamus there is no recognizable anatomical lesion of this area

PRECOCIOUS PSEUDOPUBERTY

Isosexual pseudopuberty is a rare disturbance in girls the cause being an ovarian tumour Granulosa cell tumours secreting oestrogen are found usually in adults but 10 per cent of these growths occur in children causing premature breast development growth of feminine body hair and irregular bleeding from an enlarged uterus The very rare and malignant chorionepithelioma causes pseudopuberty but kills within a year

In boys congenital adrenal virilism is the most common cause of precocious pseudopuberty more rarely an interstitial cell tumour of the testis secreting androgens causes intensive growth of male secondary sex characters with the obvious physical sign of a tumour in the scrotum The tumour may be benign or malignant the urinary 17 ketosteroid excretion is extremely high

Heterosexual precocity is usually adrenal in origin as described in the appropriate section (see page 105)

DIAGNOSIS

The possibility of induced precocity should not be forgotten as synthetic oestrogens prescribed for mother may well be within the reach of an inquiring child whose experimental eating will result in breast hypertrophy with deep pigmentation of the nipples There are also two non-endocrine conditions which simulate precocity in girls The first idiopathic breast hypertrophy can occur at an early age is predominantly unilateral and not associated with other signs of maturation The second congenital hypertrophy of the clitoris may be due to virilization of the mother during pregnancy but is not found with any endocrine disturbance of the child

(B) *Pseudopuberty*

(1) Isosexual

(*a*) Gonadal	Girls—Ovarian granulosa cell tumour Boys—Testicular interstitial cell tumour
(*b*) Adrenal	Boys only—Congenital hyperplasia or tumour

(2) Heterosexual

Adrenal	Girls—Virilizing tumour or hyperplasia Boys—Feminizing tumour

Premature isosexual development is about three times more common in girls than in boys The majority of the female cases are examples of benign constitutional precocity a condition which accounts for only 20 per cent of male cases It follows that precocious sex maturation in girls is seldom due to a serious lesion but sexual precocity in boys must be considered with gravity

Constitutional Precocious Puberty

The term constitutional is cumbersome and not explanatory It is meant to describe the normal process of sexual maturation (i e true puberty) which starts at an age which is definitely below the normal average for the onset of puberty Hence the physiological mechanisms of this type of puberty are perfectly normal but come into action prematurely The reason for this is quite obscure probably representing the extreme in biological variation around the mean age for the normal onset of puberty This type of precocity is seen predominantly in girls only 10 per cent of cases being male

Sexual development proceeds along normal lines but often at a rather slow tempo The growth of pubic hair and breasts is followed by the appearance of axillary hair and menstruation Somatic growth is also accelerated It is important to realize that ovulation will occur and conception is possible although the general outlook of the patient is still childlike

Lesions of Hypothalamus

The importance of the hypothalamus in the onset of puberty has been described already (see page 12) Lesions causing sexual precocity affect the posterior hypothalamus but the area involved is not sharply demarcated as in diabetes insipidus Severe neurological disturbances accompany the sexual development in the case of basal meningitis Tumours in this region will sooner or later cause internal hydrocephalus Cortical destruction

CHAPTER IX

THE TESTIS

The testis grows in embryo from the genital ridge adjacent to the mesonephros gradually descending as it becomes differentiated until it lies at the deep inguinal ring by the seventh month of gestation At this time the testis rapidly traverses the inguinal canal to reach the scrotum The mechanism of this descent is unknown and there is no evidence to indicate a primary hormonal stimulus

At birth the testicular tubules have a small lumen with many undifferentiated cells in the enclosing wall During childhood the cells of the tubule differentiate into layers spermatogonia are identifiable but inactive Tubular growth and maturation starts at puberty the mass of the gland increases greatly hormonal production is initiated and the process ends with full spermatogenesis

The endocrine activity of the testis resides in the connective tissue which with blood vessels and nerve fibres fills the space between the tubules The cells responsible for hormone production are the Leydig cells identifiable by an accumulation of lipids during puberty The hormone produced is testosterone which influences the growth of male sex characters and somatic development The hormone is metabolized probably by the liver to 17 ketosteroids which are excreted in the urine

Some oestrogen is produced by the testis probably by the Sertoli cells which are large pyramidal cells attached to the inner surface of the basement membrane of the tubule It is further suggested but by no means proven that the tubules produce a hormone designated inhibin which suppresses the secretion of pituitary gonadotrophins

Control of Testicular Maturation

The anterior pituitary controls the cellular development hormone production and spermatogenesis of the testis by the secretion of two gonadotrophic hormones The initiation of sexual maturation depends on the gonadotrophin secretion at the time of puberty It is known that gonadotrophins are present in the anterior pituitary for some time prior to their release The exact time for their secretion and the consequent onset of gonadal activity appears to be determined by the hypothalamus

The gonadotrophins are protein in structure but although the two

The early appearance of pubic hair in girls is part of both iso- and heterosexual development Absence of breast hypertrophy and the presence of an enlarged clitoris indicates heterosexual precocity confirmed by the finding of excessive urinary 17 ketosteroids Isosexual precocity is associated with breast growth and is usually of constitutional origin the likelihood of this event increases as the age of the patient nears that of normal pubescence Organic cerebral lesions are detectable by the associated neurological abnormalities and the rare case of ovarian tumour is usually detectable by abdominal palpation There is no indication for routine abdominal laparotomy in cases of precocity

The distinction of true from pseudopuberty in boys is made on examination of the testis which fails to develop in pseudopuberty A testicular tumour must not be mistaken for normal enlargement of the testis Precocious true puberty is usually due to organic cerebral disease with its attendant neurological signs

In both sexes the degree of somatic precocity as indicated by serial measurements of height and radiological evidence of epiphyseal maturity is confirmatory evidence of the hormonal disturbance Apart from the usefulness of 17 ketosteroid estimations other hormonal assays are of academic interest rather than a practical necessity

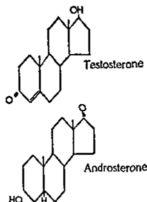
TREATMENT

Treatment obviously depends on the causative lesion. Therapy for adrenal virilization of both sexes has been described already (page 109) Tumours of the adrenal gonad or in contact with the hypothalamus must be removed if possible

The common instance of constitutional precocity requires no therapy early sex development of this type is perfectly normal and of no consequence in adult life activity usually ending with a late menopause However the child s parents require firm guidance on the handling of sexual precocity Although adult emotions are not found organic sex maturation gives rise to an increased eroticism and often frequent masturbation It must not be forgotten that childish explorations of sexual activity may lead to pregnancy in a girl with precocious puberty The parents should understand the essential normality of early puberty and not adopt a prudish attitude Boarding schools are on the whole not advisable for the precocious child who is best supervised in the home by tolerant parents

when the larynx enlarges at puberty are all signs of normal testosterone secretion

In its general metabolic action testosterone is a powerful stimulant of protein anabolism Hence in the young it causes an increase in muscle bulk with a rapid rate of upward growth This is curbed by an increase



Test cular Androgens

in the speed of epiphyseal closure It is obvious that a lack of testosterone during a phase of normal growth will result in poor muscle bulk and eventual gigantism from delay in epiphyseal closure

Hypogonadism

As endocrine function resides in the interstitial tissue of the testis failure of spermatogenesis as a sole lesion cannot be termed a variety of endocrine hypogonadism However full spermatogenesis is not possible without normal endocrine function of the testis so that the demonstration of sperm formation is proof of normal gonadal function

The normal gonad does not function until puberty hence it is illogical to diagnose hypogonadism prior to the age of sexual maturation Of course pathological lesions which will eventually cause hypogonadism can be present at an early age As a failure of sex maturation is so different clinically from hypogonadism arising in a fully matured male it is wise to distinguish puberal from adult hypogonadism The term puberal hypogonadism includes testicular lesions present prior to puberty but it is preferred to the commonly used term prepuberal hypogonadism which implies a disorder of function that is present at a time when the normal

hormones have their individual chemical properties their structural formulae are not known However the action of each hormone is known and determines their nomenclature Follicle stimulating hormone (F S H) a name derived from its action in the ovary promotes the maturation of the tubule and spermatogenesis Luteinizing hormone (L H) in the male more appropriately called interstitial cell stimulating hormone (I C S H) is responsible for the development and hormone production of the Leydig cells The two gonadotrophins have a complicated synergism the action of F S H being greatly enhanced by small quantities of L H It is also probable that a certain amount of androgen is necessary for optimum response of the testes to gonadotrophins

Two gonadotrophins of extrapituitary origin have been used for their effect on the testis Chorionic gonadotrophin produced by the human placenta mimics the action of L H on the Leydig cells a gonadotrophin prepared from pregnant mares serum has a weak effect on the tubules but the intensity of its action is not comparable to F S H and the hormone is strongly antigenic resulting in severe antibody reactions

The Action of Testosterone

Anatomically speaking the endocrine function of the testis is restricted to a few cells of the interstitial tissue while the bulk of the organ is composed of gametogenic tissue However the testosterone elaborated by these cells has a profound influence on the male body determining the development of secondary sex characters and influencing somatic growth.

Testosterone institutes and sustains the pubertal growth of seminal vesicles prostate scrotum and penis As a corollary of this the volume of the ejaculate and erection of the penis are dependent on adequate testosterone If in adult life the male is deprived of testosterone atrophic changes take place in the organs enumerated but these are seldom clinically obvious compared to the major signs of failure of penile erection and gross diminution in the volume of ejaculate

The effect of testosterone on the testis itself appears to vary according to the amount of hormone available Small amounts of testosterone are necessary for full testicular growth and spermatogenesis Larger amounts inhibit spermatogenesis and very large amounts at the stage of puberty inhibit development of the testis

The growth and maintenance of male secondary sex characters are controlled by testosterone The growth of axillary and pubic hair with its characteristic extension toward the umbilicus the bitemporal recession of scalp hair the growth of facial hair and breaking of the male voice

During the years of adolescence the patient is short for his age because his contemporaries experience the normal growth spurt of puberty However growth continues in the absence of testosterone proceeding throughout the twenties until the patient may be exceptionally tall with abnormally long arms and legs Radiography of the epiphyses indicates greatly delayed closure The unfused epiphyses are particularly likely to slip indeed a slipped epiphysis after the age of twenty is in itself pathognomonic of hypogonadism

As with other people eunuchoids may be fat or thin However those who are thin appear asthenic because of poor musculature and those who are fat accumulate adipose tissue around the hips pubis and pectoral region

The character of the eunochoid is timorous and retiring mainly due to realization of his physical abnormality but partly from lack of testosterone Often these patients seek advice for various neurotic symptoms rather than for their genital inadequacy Lack of libido failure of penile erections and absence of seminal fluid and spermatogenesis add to infertility and impotence in all severe cases

Incomplete failure of Leydig cell function provides many grades of eunuchoidism In addition the sensitivity of tissues to androgen is variable as illustrated by the differences in beard growth and body hair seen in normal fertile men Appraisal of maleness in any patient must take these factors into account

The most interesting type of partial hypogonadism is that found with hyalinization of the tubules and apparent histological normality of the Leydig cells Testosterone production is only moderately impaired as judged by the degree of sexual development but gynaecomastia is present and the urinary excretion of gonadotrophins is increased to the high level associated with total testicular destruction This clinical picture has been designated Klinefelter s syndrome after the author who first described it but the dignity of a syndrome is not merited by a disturbance which is merely a grade of hypogonadism Indeed all grades of eunuchoidism occur the severe grade is not associated with gynaecomastia while palpable breast tissue is not infrequently seen with the lesser grades Moreover administration of androgen to a severely affected eunuchoid may be followed by partial growth of secondary sex characters and the appearance of gynaecomastia

Adult Hypogonadism

Regression of fully developed male sex characters is only partial if the testes are destroyed or removed or if gonadotrophin secretion fails

testis has no function The clinical picture of hypogonadism can be termed eunuchoidism reserving the name eunuch for those who have experienced surgical castration Hypogonadism can be classified as follows

TESTICULAR FAILURE – HYPOGONADISM

A Primary Testicular Lesion (Hypergonadotrophic)
  (1) Predominantly Tubular
  (2) Predominantly Leydig Cell
    (*a*) Congenital – agenesis
      maturation arrest
    (*b*) Acquired – aetiology usually unknown
      specific fevers
      mumps orchitis (only at puberty or later)
      Orchidectomy

B Primary Pituitary (or hypothalamic) Lesion (Hypogonadotrophic)
  (1) Part of total pituitary failure
  (2) Selective failure of gonadotrophin secretion
  (3) Suppression of gonadotrophin secretion
    (*a*) Chronic debilitating disease or malnutrition
    (*b*) Hormonal – oestrogens in excess
      androgens in excess

CLINICAL PICTURE

Puberal Hypogonadism

Puberal testicular failure is far more common than the adult variety although many of its victims do not seek medical aid until they are adult in years The degree of Leydig cell failure varies If the failure to secrete testosterone is complete the patient preserves a childlike look into his later years The testes never enlarge and may not even be palpable in the scrotum which remains small The penis fails to enlarge from its pre-puberal size and erections do not occur At the most a few fine hairs spread sparsely over the pubic under the influence of adrenal androgen are the only evidence of body hair The scalp hair extends in a straight line across the frontal area without the bitemporal recession characteristic of the normal adult male The face remains hairless and retains the fine textured skin of the child together with a pallor which fails to turn brown under sunlight As the years advance very fine wrinkling or crow s feet surround the eyes and often appear around the upper lip at the nasolabial fold

instances of sexual infantilism are not due to primary endocrine disease but to inhibition of gonadatrophic secretion by some prolonged illness Malnutrition either dietetic or from malabsorption, plays a large part in the aetiology of this condition but chronic infections cyanotic congenital heart disease or chronic renal failure may delay sexual development. The presence of such diseases or the past history of chronic illness often explains hypogonadism of pituitary origin Léss common is a selective failure of gonadotrophin secretion with otherwise normal pituitary functions Such a diagnosis can only be confirmed by assay of the urine for its content of F S H or the administration of chorionic gonadotrophin, which will result in an increased 17 ketosteroid excretion and the secretion of androgen, as judged by penile and secondary sex character maturation The distinction of such lesions from primary testicular failure when the gonadotrophin content of the urine is excessively high and there is no response to injected chorionic gonadotrophin is not essential to treatment for which androgen administration is preferable in both types of hypogonadism

The adult may present with a puberal failure of maturation or with hypogonadism arising in a previously normal matured male In the latter case atrophy of secondary sex characters is not an early sign loss of libido and failure of penile erection is the main complaint Hypogonadism must therefore be distinguished from other causes of impotence evidence of normal spermatogenesis and volume of ejaculate precludes a diagnosis of hypogonadism. Primary testicular lesions are evident on palpation and lesions secondary to pituitary failure are found in the presence of severe pituitary disease This does not mean that panhypopituitarism is present for the commonest lesion is the chromophobe adenoma of pituitary causing visual disturbance and hypogonadism Other conditions may inhibit gonadotrophic secretion by an excess of circulating oestrogen The administration of stilboestrol for prostatic carcinoma is a clear example of medically induced testicular failure Cirrhosis of the liver when hepatic inactivation of natural oestrogen is inefficient causes breast enlargement and testicular atrophy Lastly haemochromatosis is frequently associated with hypogonadism either because of fibrosis of the testis or cirrhosis of the liver

TREATMENT

Androgen replacement therapy is very effective in terms of sex development and virility but the prognosis in terms of fertility is extremely poor Assessment for therapy depends on the age of the patient, the degree

Diminution of testicular size is apparent and the shape and feel of the testis may reveal a causative pathological lesion Facial and body hair remains but the rate of beard growth diminishes Many months later beard growth may cease and body hair becomes scanty but this is usually in association with panhypopituitarism rather than primary testicular failure Penile size seldom diminishes but erections do not occur and the volume of ejaculate becomes minute Libido and potency often fail but are sometimes retained after castration contrary to the precepts of the harem A feeling of languor and loss of muscular strength are associated with the diminished androgen production

DIAGNOSIS

With puberal lesions the degree of testicular and sexual development is obvious on inspection but the necessity for treatment and the prognosis demand recognition of the causative lesion In younger patients (13-15 years old) the diagnosis of hypogonadism is uncertain because of the variation in time of onset for normal puberty A physiological delay in puberty may be present up to the 16th year the subsequent sex development being normal which should make the physician chary of hormonal therapy before the age of fifteen years However the boy who is not in puberty at the average age for normality is exposed to the ridicule of his companions which is likely to injure his social adjustment For this reason a very delayed puberty should be treated as transient hypogonadism rather than left alone for nature to take its dilatory course

The diagnosis of primary testicular failure is obvious if the testes have been removed by surgery or trauma A testes lying within the sac of an inguinal hernia is most likely to be the victim of surgical repair in childhood The absence of testes from the scrotum or from any palpable position in the inguinal region presupposes a testicular defect probably agenesis Primary atrophy of scrotal testes whatever the cause is evident on palpating minute hard organs as compared to the softer bean-shaped testes which have failed to mature The presence of gynaecomastia in association with eunuchoidism points to a testicular lesion The family history should also be investigated for arrest of testicular maturation may be congenital and present in more than one sibling

Hypogonadism may be part of panhypopituitarism in which case the diagnosis is clear from the associated signs This condition is very rare compared to the large groups of sexual infantilism in which hypogonadism is associated with small stature Of course some degree of growth failure is directly due to the absence of testicular androgens Many

paration (testosterone phenyl propionate 50 mg every 3 to 4 weeks) or methyl testosterone tablets The choice depends largely on the patient s preference and the convenience of the method Large initial doses are not indicated for patients below the age of 18 years

A gratifying advance in emotional and social stability usually accompanies the physical changes induced by testosterone but those patients who are mentally feeble as well as hypogonadal may exhibit eroticism and antisocial behaviour if treated with large doses of androgen For this reason the speed of physical development desirable must be judged in the light of the patient s intelligence

Successful therapy for eunuchoidism is often followed by the patient s request for advice on marriage He should be told that a full sex life is possible with continued therapy but fertility is extremely unlikely A frank discussion with the fiancée is an advantage which may pave the way for a successful marriage and adoption of children It is important to realize that spermatogenesis may occur in rare instances either as a very late natural event or perhaps induced by androgen Although this is a great rarity it should be allowed for by pronouncing the patient s fertility to be an unlikely rather than an impossible fact If conception does indeed take place when the husband has been told authoritatively of his inability to conceive the natural reaction is to accuse an innocent wife of infidelity

Cryptorchidism

Failure of testicular descent is not specifically an endocrine problem Indeed it is the opinion of some surgeons that hormonal therapy is never indicated although there is good experimental and clinical evidence of descent induced by chorionic gonadotrophin (mimicking the luteinizing hormone of the pituitary) True cryptorchidism must be differentiated from scrotal testes which are retractile by the action of the cremasteric muscle into the inguinal region A warm examining hand and gentle downward manipulation will reveal the retractile testis It is also true that testicular descent occurs spontaneously after birth The incidence of cryptorchidism at birth has been estimated as 10 per cent at puberty it is 2 per cent and in manhood about 0 2 per cent Therefore the chance of spontaneous descent is high and any endocrine therapy may have been associated with a natural cure

Imperfect descent is associated with bilateral abdominal testes bilateral inguinal testes or ectopic testes either unilateral or bilateral In the first instance no testicular tissue is palpable in fact the organ may be agenetic

of skeletal maturity as revealed by radiography of the epiphyses, and the type of testicular lesion Androgen therapy before the age of 14 years is quite unwarranted in terms of hypogonadism, but is essential after the age of 20 years If development is proceeding when the patient presents between the ages of 14 and 20 years it is wise to observe natural maturation over a period of six months to gauge the necessity for therapy Bone age is only of importance in younger patients suitable for treatment when some assessment can be made of the possible degree of skeletal growth prior to closure of the epiphyses under the influence of administered testosterone Obviously the short boy with little delay in epiphyseal closure is likely to remain stunted if large doses of testosterone are given.

Patients with chronic illness require treatment of the causative lesion rather than of the associated hypogonadism Androgen therapy is only an adjunct in these circumstances and should not be used to excuse a failure of diagnosis In cases of delayed puberty or pituitary infantilism not associated with other lesions chorionic gonadotrophin is the logical treatment in doses of 500 i u injected twice or thrice weekly The stimulation of testosterone production by this means is often suboptimal and good results may be obtained by the use of small doses of testosterone alone Enlargement of the testes on testosterone therapy indicates the onset of spontaneous development whereupon hormone therapy can be discontinued On the other hand eunuchoidism in the adult should be treated initially with large doses of testosterone smaller doses for maintenance being given when sexual maturation has been achieved *Gynaecomastia is never diminished but sometimes increased by androgen* therapy

The choice of available *testosterone preparations is* wide testosterone propionate 25 mg injected intramuscularly twice weekly is roughly comparable to methyl testosterone absorbed sublingually in a daily dose of 15-25 mg Long acting esters of testosterone or the injection of a microcrystalline suspension cuts down the number of injections required for adequate therapy Implantation of testosterone pellets in the subcutaneous tissue of the abdominal wall provides a long-term therapy which requires renewal every 6-9 months Each 100 mg pellet provides roughly the same androgen per day as 10 mg testosterone propionate injected twice weekly

Initial therapy is provided best by testosterone propionate 50 mg twice or thrice weekly Methyl testosterone 50 mg *daily sublingually* produces about the same effect. Maintenance therapy should be conducted with *implantations* the use of a long-acting intramuscular pre-

of chorionic gonadotrophin In many the urinary excretion of this hormone is as marked as in normal pregnancy and can be assayed easily by the routine pregnancy tests Oestrogen may also be secreted some degree of gynaecomastia being quite common The Leydig cells of the testis opposite to the tumour may become hyperplastic in response to the excessive gonadotrophic stimulus

Interstitial or Leydig Cell Tumour

This androgen-producing tumour has usually been found in prepuberal boys giving rise to precocious sex development (see page 135) Spermatogenesis does not occur The tumour is usually palpable but by no means always easy to diagnose on palpating the testis 17 ketosteroid estimations have shown results varying from relatively enormous amounts for a child to a minimal increase The diagnosis in distinction from adrenal precocity is dependent on the enlargement of the testis and the identification of the tumour

Sertoli Cell Tumour

This is the rarest of all giving rise to gynaecomastia and recession of male characters because of its capacity to secrete oestrogen The fact that a tumour of Sertoli cells can produce oestrogen is the main reason for suggesting that these cells secrete oestrogen as a normal function It appears to be a tumour of adult life but there is not enough data available to be more dogmatic

and any form of treatment is of no avail In the second spontaneous descent may occur but in the third the ectopic position prevents normal descent and surgical interference is indicated

A testis retained above the scrotum appears to be unharmed until the age of puberty After that time the tubules degenerate rapidly although Leydig cell function is usually normal Some authorities maintain that the degenerative process is initiated in early childhood but most argue that treatment of any kind should be left until the age of 10 years but on no account should be delayed until signs of puberty are present

The physician is faced with the problem of the correct treatment when spontaneous testicular descent has not occurred by the age of 10 years Unilateral maldescent the opposite testis being well down in the scrotum, indicates an ectopic position requiring surgery Bilateral cryptorchidism with testes palpable in the inguinal canal responds well to chorionic gonadotrophin It may be argued that spontaneous descent would have occurred but the extremely poor prognosis for fertility if nothing is done and puberty starts, warrants a preliminary trial of gonadotrophin followed by surgery if descent is not obtained

Chorionic gonadotrophin 500 i u injected intramuscularly three times a week for 24-36 injections provides an adequate course If descent occurs during therapy the injections may be stopped The induced secretion of testosterone by the testis is revealed by a spurt in upward growth and penile development with the appearance of pubic hair If these signs are present without descent of the testes surgery is indicated immediately Absence of sex development justifies prolongation of hormone therapy Excessive penile growth with troublesome priapism is an indication to stop therapy or to alter the frequency of injection to 500 i u once a week.

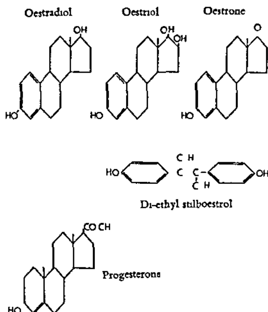
When no testicular tissue is palpable the prognosis is poor A viable scrotal testis is unlikely to result from surgery and hormone therapy in itself is ineffective The best course is to give chorionic gonadotrophin which may result in the testis becoming palpable and then proceeding to surgical intervention The late results of surgery are not encouraging from the point of view of fertility

Tumours of Testis with Endocrine Function

With the exception of teratomas which seldom cause clinical evidence of hormonal disturbance functioning tumours are of the utmost rarity

Teratoma

These growths usually found in young adults secrete variable quantities



Oestrogens

When the menstrual cycle is established the rate of oestrogen secretion increases from the time of menstruation to reach a peak at the time of ovulation. During this phase the hormone causes proliferative changes in the endometrium which becomes much thicker and hyperaemic. Subsequent changes to a secretory endometrium are dependent on progesterone In the second half of the menstrual cycle oestrogen secretion which diminishes sharply after ovulation, increases to reach a second peak just prior to menstruation. Administration of oestrogen during the first half of a normal menstrual cycle inhibits ovulation and delays the onset of menstruation However no change is observed if oestrogens are given only during the second half of the cycle

Oestrogen administered to an ovariectomized woman causes proliferative development of the endometrium which will become polypoid hyperplasia if the dose is high enough During continuous oestrogen therapy there will be intermittent bleeding from the endometrium when proliferation has taken place However if therapy is stopped considerable uterine bleeding occurs within a few days cyclical therapy is followed by regular bleeding on withdrawal of oestrogen The effect of oestrogen on uterine bleeding is probably due to spasm of the spiral arteries with sub-

CHAPTER X

THE OVARY

THE anatomy and pathology of the female genital tract lies in the province of gynaecological textbooks to which this chapter is a supplement not a substitute This section illustrates the controlling and integrating function of the endocrine system on the structural changes which proceed through puberty to the establishment of a menstrual cycle and culminate in pregnancy Apart from its gametogenic function the ovary, as an endocrine organ induces maturation of the accessory sex organs and secondary sex characteristics and creates the physiological environment required for pregnancy

The endocrine activity of the ovary starts at puberty and ceases at the menopause Throughout its active life it secretes two types of hormone oestrogenic and progestational which in their phasic secretion are responsible for the monthly preparation of the endometrium for pregnancy A true menstrual cycle must include ovulation as well as the endometrial changes Failure of conception is followed by the breakdown of the prepared endometrium at menstruation described by Hippocrates as the bloody tears of a disappointed uterus

OESTROGENS

Physiology

Oestrogens so called from their power to induce oestrus in castrated animals are secreted by the granulosa cells which surround the ripening follicle Although ovarian oestrogens are of prime importance the adrenal cortex contributes some oestrogen and during pregnancy the placenta is a rich source of these hormones

Oestrogens induce and maintain the maturation of Mullerian duct derivatives secondary sex characters and the breast They also have a general metabolic effect causing retention of nitrogen calcium sodium and water in this they are less potent than androgens More specific to sex function is the moulding of the skeleton and the deposition of subcutaneous fat in feminine sites under the influence of oestrogen which also affects epiphyseal closure Pubertal growth of vulva vagina uterus and fallopian tubes is controlled by oestrogen The growth of axillary and pubic hair is not solely controlled by this hormone and is influenced strongly by adrenal androgen

The potency of oestrogens has been compared in women by determining the dose required to reach the threshold level for uterine bleeding the results are approximately correct for other physiological effects The effect of stilboestrol 1 mg is equalled by 0 05 mg of ethinyl oestradiol or 4 mg of dienoestrol The equivalent daily intramuscular dose is about 0 5 mg of oestradiol benzoate A low dose of oestrogen is in the range of 0 1-1 0 mg a moderate dose 1-3 mg and a high dose 5-15 mg of stilboestrol daily (or the equivalent in other oestrogens)

PROGESTINS

Physiology

Compared to oestrogens progestational hormones have a limited field of action affecting the breast and preparing an already oestrinized endometrium for pregnancy If progestin is administered in the presence of oestrogen the endometrium is converted from the proliferative to the secretory phase bleeding occurs when progestin dosage is stopped In the absence of oestrogen progestin has no effect on the endometrium and there is no bleeding when therapy stops Thus a short course of progestin can be used as a rough assay of the patient s endogenous oestrogen production If uterine bleeding appears after the course one can infer that oestrogen secretion was present

Luteinized theca cells of the corpus luteum secrete progestin In pregnancy the placenta provides a rich source of this hormone The adrenal cortex may also secrete progestational compounds for progesterone is a key substance in the biosynthesis of adrenal steroids

Chemistry

The progestational compound of the ovary has been identified as progesterone The metabolic pathways of this hormone are still obscure but great attention has been paid to the urinary excretion of pregnanediol which is certainly a metabolite of progesterone but only accounts for about 15 per cent of the parent hormone As pregnanediol is also excreted in cases of adrenal virilism due to a disorder of biosynthesis relating to progesterone this metabolite is an inaccurate guide to ovarian progesterone production The progressive increase in the excretion of pregnanediol as pregnancy advances reflects placental function

Progesterone is available for implantation in pellet form or in oily solution for intramuscular injection When given by mouth it is almost inactive but the synthetic progestational compound ethisterone (ethinyl testosterone) is suitable for oral use Comparison of potency indicates

sequent breakdown of the endometrium However, the bleeding is not simply the result of a falling oestrogen concentration as it can be stopped by a rapid rise in circulating oestrogen. A convenient explanatory hypothesis is the concept of a threshold level of oestrogen concentration at which bleeding occurs only to cease if the concentration of hormone is raised above or falls below the threshold Thus one may cause uterine haemorrhage by stopping oestrogen administration or stop the haemorrhage by giving oestrogen

None of these observations are strictly applicable to normal menstruation in which bleeding occurs from a secretory endometrium Certainly oestrogen secretion diminishes rapidly at the time of menstruation, but the actual shedding of the endometrium probably depends on a subtle interplay of progestin and oestrogen concentrations or on the metabolites of these hormones

Chemistry

Oestrogens can be classified as naturally occurring partially synthetic or synthetic The natural hormones of the ovary are oestradiol oestriol and oestrone oestradiol is interconvertible with oestriol from which is formed oestrone The comparative potency of these three hormones varies according to the method of administration and the type of assay by any test oestradiol is the most potent All three oestrogens are inactivated by conjugation in the liver and subsequently excreted in the urine The role of the liver has clinical importance in that signs of hyperoestrinism may be found in chronic hepatic disease

Natural oestrogens were very costly for therapeutic use and inactive on oral administration Hence the discovery of synthetic non-steroid oestrogens derived from stilbene proved a major advance being of low cost and fully potent when given by mouth Diethylstilboestrol is the best known of these compounds but its potency has been greatly exceeded by the more recently prepared partially synthetic compound ethinyl oestradiol The main toxic effect of these compounds is nausea and vomiting The ratio of therapeutic to toxic dose varies with the compound stilboestrol being far more likely to cause vomiting than ethinyl oestradiol which in turn is rather more toxic than dienoestrol It is a curious fact that pregnant women can tolerate very large doses without toxic effect The efficacy of oral administration makes parenteral therapy unnecessary unless the patient is particularly sensitive to the toxic effects of oral oestrogen Under these circumstances oestradiol benzoate (esterification delays absorption) should be given by intramuscular injection

pause as the physiological activity of the ovaries is confined to the period between these two events The clinical picture of hypogonadism is determined by the age at which failure of function occurs Maturation is arrested by early failure but late failure is associated with changes akin to the normal menopause

Sexual Infantilism

The persistence of amenorrhoea neuter body contours and infantile genital tract together with the absence of breast development and scanty body hair indicate sexual infantilism. The physical stigmata are associated with absent libido and emotional immaturity The causes are

Gonadal lesions – Agenesis
Maturation arrest
Bilateral oophorectomy

Delayed puberty (without functional disturbance)

Pituitary lesions – Panhypopituitarism
Selective gonadotrophin deficiency
Suppression of gonadotrophin secretion
Malnutrition
Chronic illness

The rare causes gonadal agenesis and panhypopituitarism, are important because of their prognostic significance Absolute sterility and permanently short stature are the inevitable consequence of gonadal agenesis panhypopituitarism indicates a severely disturbed metabolism possibly with a space filling lesion in the area of the pituitary The essential points of these syndromes have been discussed in the appropriate sections (page 133 and page 30)

Diagnosis in the majority of cases poses three questions is this delayed puberty is this gonadotrophic or is it ovarian failure? Chronic illness or malnutrition is apparent clinically short stature being a common accompaniment (see aetiology of dwarfism and male hypogonadism page 28 and page 14[illegible]) It is sometimes easy to overlook steatorrhoea or inadequate food intake as in mild anorexia nervosa Hypothyroidism can also present as delayed sexual development in the absence of clear general stigmata Severe illness in childhood may retard development for a short while leaving the patient maturing at a normal rate but consistently behind her contemporaries so that there is a physiological delay in the onset of puberty In perfectly normal girls there is a wide range for the

that 6 mg of ethisterone by mouth is equivalent approximately to 1 mg of injected progesterone

Ovarian-Pituitary Interaction

The menstrual cycle is governed by a sequence of reactions between the ovary and anterior pituitary, with an overall control from the hypothalamus For some time prior to puberty gonadotrophins are elaborated by the pituitary but not released until hypothalamic stimulation initiates sex development During adult life abrupt cessation of menstruation is often associated with emotional disturbance (i e as an early sign in anorexia nervosa) probably due to hypothalamic interference with pituitary function

The pituitary influences the ovary by the secretion of three distinct gonadotrophins Follicle stimulating hormone (F S H) causes growth of the ovarian follicle with ripening of the granulosa cells and theca interna Luteinizing hormone (L H) causes growth of the corpus luteum and cholesterol storage within it Ovarian hormone production requires a mixture of F S H and L H for oestrogen secretion and a mixture of L H and luteotrophin (probably identical with prolactin) for progesterone secretion Synergism is demonstrated by follicular growth in which small amounts of L H greatly enhance the action of F S H

At the beginning of a menstrual cycle oestrogen stimulates release of F S H which together with L H increases the rate of oestrogen secretion As the concentration of oestrogen rises the output of F S H is depressed until the ratio of F S H /L H changes in favour of L H At some critical moment in this changing ratio ovulation occurs in response to the gonadotrophic stimulus The developing corpus luteum stimulated by L H and luteotrophin secretes progesterone at an increasing rate and this suppresses the output of F S H until the F S H /L H ratio is shifted back in favour of F S H It will be noted that oestrogen according to its concentration can stimulate and depress F S H secretion in high dosage it also inhibits ovulation by disturbing the critical F S H /L H ratio required It has little effect on L H in contrast to androgen which suppresses L H rather than F S H secretion Thus the use of androgen to inhibit gonadotrophin secretion in women can be of only limited use other aspects of its action depending on antagonizing oestrogen action on the target organ

Female Hypogonadism

A diagnosis of hypogonadism can be made only in patients who are over the normal age for puberty and under the normal age for the meno-

and secondary sex characters have advanced well towards maturity the dose of oestrogen should be reduced to the lowest level which causes withdrawal bleeding Some authorities prefer to add ethisterone 10-20 mg daily for the last 7-10 days of oestrogen administration, thus mimicking true ovarian function. Such a combined course is more physiological than oestrogen given alone but the induced bleeding is still artificial and sterility still present The great value of treatment lies in the physical maturation to womanhood, coupled with a deepening of the emotions which will sustain a normal married life with satisfactory sexual intercourse When adequate maturity has been reached there is no point in continuing therapy purely for the sake of cyclical uterine bleeding All treatment should be stopped for a few months in case a spontaneous natural menstrual cycle will develop It is most likely that this will not be the case so that resumption of treatment is based on the need if any to maintain the maturity of the body The patient should be aware of the merits and limits of therapy knowing that no harm results from amenorrhoea and realizing the almost certain condition of sterility Of course these facts should be communicated with sympathy only when the final prognosis becomes apparent

ADULT HYPOGONADISM

Abrupt cessation of ovarian activity is commonly due to surgical or radiation castration and is followed by symptoms in the majority of cases Hot flushes are frequent and distressing the lower genital tract atrophies leading to dyspareunia Similar symptoms are experienced by patients who undergo a premature spontaneous menopause an event usually associated with a late menarche Ovarian failure secondary to lesions of the anterior pituitary is accompanied by genital tract atrophy but hot flushes do not occur indicating that this vasomotor instability is connected with a rising titre of gonadotrophins rather than a diminishing oestrogen secretion.

The physiological ovarian failure of a normal menopause is a gradual process which is without ill effects in the majority of patients Some women, obedient to folklore insist that a variety of symptoms are necessary at the change but the basis of their complaint is neurotic rather than endocrine A few patients suffer symptoms related to ovarian failure or the additional disturbance of some facial hirsuties with recession of scalp hair probably caused by adrenal androgens unopposed by ovarian oestrogen The same mechanism by stimulating the clitoris can produce increased libido during the menopause

age at which puberty starts an onset later than the average is termed delayed puberty although it is a physiological phenomenon within the variation of normality A fifteen-year-old girl of normal stature who is perfectly healthy apart from the absence of sex maturation is likely to be an example of delayed puberty especially if there is a family history of such an event The probability of this diagnosis diminishes as the patient's age increases In doubtful cases a six to nine-month period of observation is the best test of diagnosis avoiding the unnecessary use of endocrine therapy

The alternative diagnosis to delayed puberty either physiological or from chronic illness is that of arrested ovarian development The distinction between primary ovarian arrest or lack of gonadotrophic stimulus is mainly academic the clinical picture being one of sexual infantilism in the absence of a demonstrable cause or associated disease The urinary gonadotrophin content is high in cases of primary ovarian failure and zero in selective failure of gonadotrophin secretion There is no ready explanation for the curious fact that the anterior pituitary can be normal in all functions except gonadotrophin secretion it may be that present tests of function are too crude to detect minor deficiencies in the secretion of other trophic hormones The only clinical distinction between hyper- and hypogonadotrophic infantilism is applicable to the group of cases rather than the individual patient a slender body with a height below average and complete absence of body hair suggests gonadotrophin deficiency compared to a normal height and scanty pubic hair in primary ovarian failure In both types epiphyseal closure is delayed but seldom to the degree common in male eunuchoids In consequence eunuchoidal gigantism is very rare although the limb length is greater than normal

TREATMENT

A delayed normal puberty requires no treatment Chronic illness associated with sexual infantilism requires therapy specific for the condition although endocrine treatment may be considered as an adjuvant Replacement therapy with oestrogen is indicated for ovarian failure even if endogenous gonadotrophins are present because the available preparations of gonadotrophins are so unsatisfactory An initial dose of stilboestrol 2-5 mg daily (or its equivalent) should be given for two months and then continued in cycles of three weeks with an intervening week free from therapy As sexual development proceeds withdrawal bleeding will occur at the end of each course of oestrogen When the genital tract

common in young women whose menstrual rhythm has never been firmly established Some degree of hypogonadism is a common accompaniment and cyclical therapy provides a reasonable chance of a normal menstrual rhythm asserting itself at a later date The same considerations apply to very irregular scanty periods in this age group However a lenient view should always be taken of such menstrual irregularities in a healthy girl below the age of 20 years observation taking the place of treatment as a spontaneous evolution of a more stable menstrual cycle is very likely to occur

A suitable form of cyclical therapy is the daily administration of stilboestrol 2 mg for three weeks adding ethisterone 20 mg daily during the last week Withdrawal bleeding will occur in the succeeding week free of treatment and the cycle is then repeated Absence of withdrawal bleeding after the first or second course of treatment is of no concern Therapy should be continued until a regular cycle is present If the haemorrhage is excessive the dose for the next cycle should be reduced to half that of the original course After three or four months of regular controlled bleeding therapy is stopped altogether to allow a natural menstrual cycle to arise If this does not occur within six months the whole treatment may be repeated but any evidence of spontaneous menstruation however irregular should be taken as an excellent sign which should not be obscured by more exogenous hormone

Hypothyroidism has been noted as a course of deficient sex maturation which will of course be associated with amenorrhoea or oligomenorrhoea in the milder grades Such menstrual irregularities may occur in patients whose appearance is vaguely suggestive of hypothyroidism but no unequivocal clinical or biochemical evidence of thyroid deficiency can be found The empirical use of thyroid extract gr [illegible] daily in these patients often proves effective

An abrupt cessation of a previously established menstrual cycle may be due to emotional factors or change in environment probably mediated by the hypothalamus Menstruation is often resumed after examination and reassurance Hormone therapy is not indicated immediately but persistence of the amenorrhoea should be treated with cyclical oestrogen and progestin for two or three courses only

It is worth remembering that a rough guide to the endogenous oestrogen production in cases of amenorrhoea is the administration of ethisterone 20–40 mg daily for five days If bleeding results then endogenous oestrogen is present but if there is no haemorrhage oestrogen deficiency can be inferred

TREATMENT

Castration should be followed immediately by the administration of oestrogen (with the obvious exception of oophorectomy to relieve carcinoma of the breast or endometriosis) which is also indicated at the menopause for hot flushes or vaginal atrophy A low dose, 0 1 mg to 1 0 mg stilboestrol daily is all that is required symptoms persisting at this level of dosage are not directly related to ovarian failure Larger doses of oestrogen are both unnecessary and harmful, causing a bloated feeling and recurrent uterine bleeding A subtle danger is the dismissal of bleeding from a uterine carcinoma as merely resulting from the oestrogen which the patient is receiving Even the recommended dose of oestrogen can cause uterine bleeding in some patients so that it is wise to allow one week free of therapy in every six There is no advantage in the use of oestrogen-androgen mixtures or in the addition of progesterone The complex psychosomatic alterations at the menopause should not be ignored for they are a reminder that hormone therapy cannot replace the understanding and guidance of a wise physician

Amenorrhoea

Amenorrhoea either primary or secondary is a matter for full clinical appraisal Endocrine therapy should never be employed as a substitute for diagnosis Moreover there is no available therapy which induces a natural menstrual cycle At the best the normal cyclical changes in the endometrium can be induced by oestrogen and progestin in the hope that a physiological menstrual cycle will begin when therapy stops

Primary amenorrhoea without an anatomical lesion may be associated with sexual infantilism or with normal maturation In the former instance diagnosis and treatment is related to failure of sex development in the latter the uterus is usually refractory to the action of normal ovarian secretion and unlikely to respond to exogenous hormones There is an outside chance that cyclical oestrogen therapy at a level of 2-5 mg stilboestrol daily for three weeks followed by a week without treatment may result in sensitization of the uterus to endogenous hormones allowing a natural menstrual cycle to evolve after therapy A full trial of this regime would cover about six months failure to establish spontaneous menstruation after this time indicates that further treatment is not worthwhile There is no point in giving artificial withdrawal bleeding purely for the sake of the haemorrhage The patient must be properly assured that no harm whatsoever results from amenorrhoea itself

Secondary amenorrhoea not due to pregnancy or organic disease is

migraine epilepsy or endogenous depression is exacerbated during the premenstrual phase A common accompaniment of their symptoms is salt and water retention leading to frank oedema The endocrine basis for the disturbance is obscure no gross abnormality being demonstrable but there is a suggestion of impaired progesterone production

However vague the aetiology the symptoms are a heavy burden to the patient Luckily therapy is often effective even if empirical Restriction of salt intake and the administration of ammonium chloride during the last half of the menstrual cycle may be successful without other measures It is more effective to combine this routine with the administration of ethisterone 10-20 mg daily over the same period of time

Ovarian Virilism

The normal ovary does not secrete a significant amount of androgen but certain tumours and hyperplasia of luteinized theca cells are capable of causing considerable virilization The androgen responsible has not been identified positively and there are possibilities that progesterone itself or its metabolites might be androgenic In contrast to adrenal virilism the 17 ketosteroid excretion is seldom raised and never markedly excessive The frequent incrimination of the adrenal as a cause of virilism does not excuse the neglect of an adequate pelvic examination in all cases Ovarian tumours are palpable on bimanual examination while adrenal tumours can only be demonstrated by complex investigations

Virilizing Ovarian Tumours

The histological characteristics of these rare tumours are so variable that a rigid classification is impossible The morphological resemblance of the tumour cells to the normal histology of the testis or adrenal cortex has led to many arguments as to the origin of the tumour and the correct classification

Arrhenoblastoma

This tumour is confined to adult life The most differentiated growths which approximate to normal testicular structure seldom possess endocrine function The grossly undifferentiated tumour with a sarcomatous appearance is nearly always associated with virilism The majority of these tumours fall into an intermediate grade a dense stroma surrounding islands of Leydig cells and tubular elements and most secrete androgen

Leydig Cell Tumour

The normal ovarian hilus contains groups of cells morphologically identical with testicular Leydig cells Tumours arising from these cells

Excessive Uterine Bleeding

Excessive uterine bleeding, with or without disturbed menstrual rhythm is commonly due to organic disease The most common endocrine lesion of this nature is an oestrogen secreting follicular cyst of the ovary However many patients exhibit no organic pelvic disorder and no consistent endometrial histology bleeding may be excessive from a proliferative or secretory phase It is hardly surprising that the uncertain aetiology of excessive haemorrhage is matched by conflicting opinions on treatment Oestrogens progestins, androgens alone or in combination have their advocates In this welter of hormonal treatment it is easy to forget the diagnostic and therapeutic use of curettage

When hormonal methods of haemostasis are deemed advisable the most effective agent to procure a rapid end to the haemorrhage is oestrogen in very high dosage Stilboestrol 5 mg (or its equivalent) every four hours will stop bleeding within forty-eight hours but is very likely to cause nausea and vomiting A smaller dose of 5 mg every eight hours can be effective and should be employed directly the higher dose causes nausea When haemostasis is achieved and no surgical measure is contemplated in the near future oestrogen therapy is continued with a gradual reduction in dose to 2 mg stilboestrol daily After three weeks oestrogen treatment is stopped Withdrawal bleeding then occurs and no further treatment is required if this is not excessive in amount or duration Excessive bleeding should be terminated by starting a three-week course of stilboestrol 2 mg daily to which ethi terone 20 mg daily is added during the last week Once again withdrawal bleeding takes place further therapy being abandoned if it is not excessive or the course being repeated if necessary

Persistent bleeding from a proliferative endometrium is especially common during puberty or near the menopause when a functioning corpus luteum is not found Immediate haemostasis is seldom required and the logical treatment is ethisterone 20-40 mg daily for five days the course being repeated monthly This is an effective measure causing secretory changes in the endometrium and a regular loss occurs which is neither excessive nor prolonged Four to six months of the treatment may be followed by normal menstrual loss

Premenstrual Tension

Many women are distressed by the mental depression general malaise and bloated feeling with tender breasts which they experience in the week preceding menstruation In others a pre-existing condition such as

in contrast to the expected atrophy is an associated sign In the adult prior to the menopause episodes of amenorrhoea punctuated by excessive bleeding is associated with the endometrial appearances of metropathia haemorrhagia In children the tumour is an exceedingly rare cause of precocious sex development

There is a sinister connection between oestrogen secreting ovarian tumours and carcinoma of the uterine body Despite extreme variation in the reported incidence it would appear that these tumours are indeed predisposing to carcinoma of the body of the uterus

are usually androgenic and small in size There is a curious clinical association with uterine fibroids some general plethora and impaired carbohydrate tolerance suggesting an adrenal rather than a testicular origin for the tumour

'Adrenal-like Tumours

The proximity in the embryo of ovary to adrenal cortex suggests that ovarian tumours composed of lipoid containing cells may originate from adrenal remnants within the ovary This suggestion receives support from the clinical picture of obesity plethora mild diabetes and hypertension which may accompany signs of virilism However on morphological grounds it is difficult to distinguish these cells from tumours of luteinized theca cells To label all such tumours adrenal-like' is a matter of convenience rather than complete accuracy

Ovarian Hyperthecosis (Stein-Leventhal Syndrome)

This is an ill-defined syndrome of enlarged sometimes cystic ovaries with a greatly thickened capsule in association with amenorrhoea male-type hirsutes obesity and occasionally enlargement of the clitoris 17 ketosteroid excretion is only slightly raised or at the upper limit of normality The essential ovarian histology is the presence of numerous small follicles surrounded by hyperplastic luteinized theca cells with occasional islands of these cells embedded in a dense fibrous stroma

The diagnostic criteria are not clear-cut and it is probable that the syndrome is indeed a very rare clinical entity Amenorrhoea with hirsutes and palpable thickened ovaries with a near normal 17 ketosteroid output are obvious essentials As great success has been claimed for the highly illogical treatment of ovarian resection the enthusiast may be tempted to perform an exploratory laparotomy on any young woman with some facial hair and amenorrhoea This is an unwarranted abuse of surgery Palpably abnormal ovaries are a more reasonable justification for laparotomy provided the patient is genuinely distressed by her appearance and sterility

Oestrogenic Tumours of the Ovary

Oestrogen producing tumours of the ovary usually consist of granulosa cells although theca cells may be present or actually dominate the histological picture These tumours may arise at any age but the majority are seen in patients over the age of 50 years In these post-menopausal cases uterine bleeding is the presenting feature A fully oestrinized genital tract

and galactopoiesis without prior pregnancy are the two other types of disorder which may come into the orbit of endocrinology

PERSISTENT LACTATION

The duration of lactation after pregnancy is largely dependent on the mother's idea of the optimum time for breast feeding persistent suckling prolongs lactation almost indefinitely When galactopoiesis continues after suckling has stopped amenorrhoea and uterine atrophy are common accompaniments The administration of oestrogen androgen or progesterone has remarkably little influence on the abnormal continuation of milk secretion Although this syndrome was noted in the last century (named the Chiari-Frommel syndrome) there is little to add in terms of investigation Recent studies have shown a raised excretion of prolactin and a lowered excretion of follicle-stimulating hormone which is probably the underlying disorder The condition is quite benign although it may persist for years The absence of effective hormone therapy makes it better to endure the discomfort of some breast secretion rather than resort to more drastic measures such as pituitary irradiation If the degree and duration of lactation is very troublesome and unresponsive to oestrogen progesterone and androgen deep X-ray to the pituitary is justified

SPONTANEOUS LACTATION

Lactation without preceding pregnancy has been described in women and men but not in children Acromegaly is the only endocrine disorder which is clearly associated with spontaneous lactation in either sex the galactopoietic activity of growth hormone has been demonstrated in animal experiments In other cases no causal factor has been demonstrated although there is a suggestion that intense emotional disturbance can initiate lactation by some hypothalamic mechanism The most common non-endocrine factor is persistent sucking or manipulation of the breast a curious form of behaviour sometimes found in gross psychotics Before looking for obscure endocrine dysfunction, it is very important to establish that the mechanical factor of suckling is absent

Gynaecomastia

The term gynaecomastia indicates enlargement of the breast tissue in men and should not be applied to deposits of fat in the pectoral area which give the appearance of an enlarged breast. Moreover hypertrophy of the male breast does not necessarily imply feminization as the condition can occur in virile men or be produced by androgens

CHAPTER XI

THE BREAST

THE female breast starts to grow in early puberty when the ovary first exerts its endocrine influence The flat areola of childhood becomes raised with the enlarging nipple surmounting it and underneath a palpable disc of breast tissue As puberty progresses the areola sinks back to the general contour of the breast leaving only the nipple protruding from it The final shape of the breast is largely due to fat deposition rather than glandular tissue in consequence the bust measurement is poor evidence of actual breast development which is indicated more truly by nipple size A clinical corollary of this is the obvious irrationality of using hormone creams to improve the shape of the breast

Full growth of the breast with subsequent lactation depends on so many hormones that it virtually requires the integrity of the whole endocrine system The primay role of oestrogen on the growth of the ductal system and nipple is associated with the growth of the lobules under the influence of progesterone which exerts its maximal effect during pregnancy Optimum breast growth also requires growth hormone adrenal glucocorticoids and thyroid hormone Galactopoiesis requires the stimulus of prolactin (luteotrophin) but the other hormones responsible for breast growth are necessary to maintain lactation The endocrine environment of breast tissue is also of importance in the growth rate of breast neoplasm There is no definite evidence to show that such malignant tumours are initiated by endocrine action but it is quite certain that the speed of tumour growth is largely dependent on the hormones acting on the breast *In these hormone dependent tumours* alteration of the endocrine environment by administration of androgen or by removal of ovaries adrenals or pituitary may slow the progress of the disease even to the stage of temporary regression

Abnormal Lactation

The various causes of inadequate or absent lactation after childbirth are not within the scope of this book It is sufficient to recall that destruction of the pituitary with post-partum haemorrhage is followed by the absence of lactation. This is the only condition in which it is clear that endocrine deficiency is the cause of lactational failure Persistent lactation

is greatly in excess of that seen when the same dose of oestrogen is given to an adult male

Puberty gynaecomastia may profoundly influence the growing boy's attitude to life He and his family fear that his body is abnormal and likely to remain so Hence treatment consists of reassurance as to the common occurrence of this enlargement its benign nature and self-limited course On no account should hormones be administered as they are likely to exaggerate the hypertrophy Similarly surgical removal of the breast is undesirable because of the natural resolution of the condition. It is surprising how large a breast will regress entirely

IDIOPATHIC GYNAECOMASTIA

This type of breast enlargement is found in virile fertile men, in the absence of any endocrinopathy The condition commonly arises during the third and fourth decade of life progressing slowly for a few months to remain static for years In nine out of ten cases the hypertrophy is confined to one breast indicating a primary abnormality of the breast tissue There is no evidence that it is a precancerous condition. The enlargement is not only embarrassing but is likely to become inflamed by rubbing against clothing The only treatment is surgical removal

EXOGENOUS OESTROGENS

The use of oestrogen therapy in the male for carcinoma of prostate or for acne has brought in its train many examples of breast hypertrophy characterized by deeply pigmented nipples and areolae Whenever oestrogens are given to a man he should be warned that breast enlargement will result The benefits of oestrogen therapy in carcinoma of the prostate far outweight the slight discomfort of gynaecomastia Oestrogen treatment of acne lost its popularity because it was a moot point whether the patient was more embarrassed by black-heads or large breasts

The manufacture of synthetic oestrogens has made gynaecomastia an industrial hazard to those men who engage in the handling and packing of these compounds Inhalation of fine dust appears to be the important route of absorption a hazard controllable by efficient ventilation systems This risk emphasizes the importance of adequate history-taking in all cases of gynaecomastia

ASSOCIATED WITH CHRONIC LIVER DISEASE

Gynaecomastia with testicular atrophy is a rare but well recognized feature of hepatic cirrhosis There is clear experimental evidence that such a lesion is due to a failure of the damaged liver to inactivate endogenous oestrogen

The histology of gynaecomastia is relatively uniform despite the variety of causes The predominant feature is proliferation of connective tissue surrounding the ducts which are increased in number lobules and acini are not hypertrophic Fluid may be present in the ducts but true milk formation is excessively rare

A classification on aetiological grounds is possible but the majority of cases fall into the groups of idiopathic breast enlargement not associated with demonstrable endocrine lesions The physiological growth of the breast at puberty is responsible for another large group of cases testicular dysfunction is the only other common cause

Classification of Gynaecomastia

In puberty
Idiopathic in adult life
Associated with intake of oestrogens
  Therapeutic
  Industrial hazard
Associated with chronic liver disease or malnutrition
Testicular dysfunction
Other major endocropathies
  Acromegaly
  Adrenal tumours (oestrogen secreting)
  Testicular tumours
  Thyrotoxicosis

Gynaecomastia of Puberty

At some time during puberty it is probable that all boys have a degree of breast hypertrophy A rubbery disc of breast tissue below the areola is palpable in about 50 per cent of boys when pubertal development is proceeding rapidly Both breasts are involved but one side is often much larger than the other A ballooning of the areola adds to the prominence of the breast By the end of puberty regression has taken place apart from a few instances which persist to early adult life

It has been suggested that an excessive secretion of sex hormones is responsible for the enlargement of the breast but as this regresses while hormone stimulation is still maximal it is more probable that a temporary increased sensitivity of breast tissue to hormone action is the real cause The experimental demonstration of increased sensitivity of secondary sex organs to a standard dose of hormone at puberty supports this view A similar experiment is observed clinically when oestrogens are administered *for pubertal acne the resultant* breast hypertrophy

APPENDIX

INVESTIGATION OF ENDOCRINE DYSFUNCTION

TESTS of endocrine function are legion yet still multiplying Some techniques are well established in most clinical laboratories others particularly those involving animals are available only in special centres In research institutes new techniques are applied to limited numbers of suitable patients but the validity of such methods is still sub judice The following brief analysis indicates the various types of investigations with the present availability of each method (G = generally available S = special centres only R = research method only)

PITUITARY

(*a*) *Posterior*

(1) Direct estimation of anti-diuretic factor in serum or urine (R)
(2) Promotion of vasopressin secretion, detected by inhibition of water diuresis
  (*a*) with intravenous hypertonic saline (G)
  (*b*) with nicotine inhaled or injected (G)

(*b*) *Anterior*

(1) Direct estimate of hormone
  (*a*) Adrenocorticotrophin level in serum (R)
  (*b*) Thyrotrophin level in serum (R and S)
  (*c*) Follicle stimulating hormone in urine (S)
(2) Indirect measure of hormone effects
  (*a*) Determination of gonadal thyroid and adrenocortical function
  (*b*) Effect on carbohydrate metabolism of intravenous insulin (adrenal also involved) (G)

THYROID

(1) Direct estimate of iodine handling by tracer doses of radio-iodine (G and S)
(2) Direct estimate of circulating hormone as protein-bound iodine (S and R)
(3) Effect of thyroid hormone
  (*a*) Basal metabolic rate (G)
  (*b*) Blood cholesterol urinary creatine (G)

The occasional association of gynaecomastia with *severe chronic malnutrition* has also been attributed to nutritional damage of the liver probably involving a lack of the Vitamin B complex

TESTICULAR DYSFUNCTION

The association of gynaecomastia and lesions of the testis has been established for many years but the mechanism involved is still obscure Surgical castrates and seriously affected eunuchoids very rarely exhibit breast hypertrophy therefore lack of testicular androgen cannot by itself affect the breast Gynaecomastia is found in the type of case described by Klinefelter (whose name is attached to the syndrome) in which aspermia is present and the testes show hyaline degeneration of the seminiferous tubules with intact Leydig cells This clinical picture merges gradually with *complete hypogonadism the greater the impairment of Leydig cell* function the smaller the degree of breast hypertrophy In some cases of eunuchoidism growth of male sex characters induced by androgen therapy is accompanied by the emergence of gynaecomastia

It is important to distinguish the young adult whose gynaecomastia is associated with testicular dysfunction from those whose physiological breast enlargement during puberty is late in its regression Biopsy of testis is a certain method of diagnosis but not a very desirable procedure Examination of the semen provides an equally clear answer in that absence of spermatozoa indicates testicular damage

Treatment is very unrewarding the only effect of androgen *being to* develop masculinity without diminishing the size of the breast or restoring fertility Surgical removal of the breast is advisable if the patient is very *distressed at his appearance*

OTHER MAJOR ENDOCRINOPATHIES

Acromegaly is an easily diagnosed condition in which hypertrophy of the breast and galactopoiesis can occur as a direct effect of growth hormone or with the possible addition of increased prolactin secretion

Thyrotoxicosis is an obscure and rare cause of breast hypertrophy

Of the rare endocrine tumours associated with gynaecomastia *those* of the testis are the most frequently seen and are all malignant *It follows* that a *very* careful examination of the testis is required whenever a man *complains* of his breasts enlarging A few instances of oestrogen secreting tumours of the adrenal cortex have been recorded in which testicular atrophy recession of male sex characters and gynaecomastia have *occurred* These are *true* feminizing tumours

hormones so that the blood pressure falls If the hypertension is not dependent on this mechanism the blood pressure does not fall

PROCEDURE

All barbiturates are withheld for at least 24 hours prior to the test The patient must be resting in bed An intravenous infusion of saline is set up and the blood pressure recorded every minute When a steady level has been obtained the adrenolytic drug is injected into the tube of the saline infusion apparatus the patient should not be aware of this injection The drug used may be phentolamine 5 mg or piperoxane in a dose of 0 25 mg / kilogram body weight The injection of 5 mg of phentolamine is preferable

Blood pressure recordings are continued every minute after the injection In two to five minutes after the injection the blood pressure will drop sharply if a phaeochromocytoma is present A fall of 35 mm Hg systolic and 25 mm Hg diastolic is diagnostic. A variation of less than 10 mm Hg is of no significance The hypotensive effect of piperoxane is short lived compared to that of phentolamine

Difficulties The test is valueless in the absence of hypertension False positives are very rare provided barbiturates have not been given False negative results do occur and there is also the possibility that the hypertension initiated by noradrenaline is no longer maintained by the concentration of this hormone

Basal Metabolic Rate

A measurement of heat production by the resting fasting patient Using a recording spirometer with carbon dioxide absorber the oxygen consumption is measured over a given time (usually 10 mins) and converted to calories by using a standard respiratory quotient The result expressed in calories per square metre of body area, is recorded as a percentage of the normal

WARD PREPARATIONS

Weight and height of patient are measured. The patient is deprived of food and drink for 12 hours (over night) prior to the test On waking the bladder should be emptied but no other activity allowed until the test is finished.

Difficulties It is extremely difficult to make the patient completely tranquil Familiarity with the machine and method (on a dummy run) together with sedation is a help Leakage of oxygen around the face-piece is the main problem presented by the apparatus Finally the tables used to

ADRENAL

(*a*) *Medulla*

(1) Direct estimate of hormone Pressor catechol amines in blood or urine (biological and chemical methods) (S and R)

(2) Destruction of circulating hormone by adrenolytic agents (G)

(*b*) *Cortex*

(1) Direct estimate of hormone 17 hydroxycorticoids in blood (S) aldosterone in urine (R)

(2) Estimation of hormone metabolites 17 ketosteroids (R) 17 ketogenic steroids (S) 11 oxysteroids in urine (S)

(3) Effects of hormone

(*a*) Kepler test (G)

(*b*) Serum electrolytes (G)

(*c*) Glucose tolerance test and response to hypoglycaemia induced by insulin (G)

GONADS

(*a*) *Testis*

(1) Direct estimate of hormone Biological assay of urinary androgens (S and R)

(2) Indirect estimate of hormone metabolites 17 ketosteroids in urine (G)

(*b*) *Ovary*

(1) Direct estimate of hormone Urinary oestrogens (biological and chemical methods) (S and R)

(2) Estimation of hormone metabolites Urinary pregnanediol as index of progesterone production (G and S)

(3) Effects of hormones

(*a*) Vaginal smear (G)

(*b*) Biopsy of endometrium (G)

Note — Responsiveness of thyroid and adrenal cortex to injected thyrotrophin and *adrenocorticotrophin can be measured to aid distinction* between primary and secondary features of these glands

Adrenolytic Test for Phaeochromocytoma

PRINCIPLE

The hypertension due to a phaeochromocytoma is dependent on a high concentration of circulating adrenalin and noradrenalin The administration of an adrenolytic drug diminishes the concentration of these

LOW CALCIUM DIET

The urinary drain of calcium due to a parathyroid tumour is often not apparent unless the patient has been on a low calcium diet for one week On the following diet urinary excretion of calcium in excess of 250 mg / 24 hours suggests the presence of a parathyroid tumour

Low Calcium diet (Approximately 120 mg ca daily)

Early a m

Tea made with distilled water
5 g sugar

Breakfast

Tea made with distilled water
10 g sugar
100 g grapefruit (fresh only)
10 g sugar
30 g Ryvita
15 g butter
15 g marmalade

Mid morning

20 mls lemon juice
15 g sugar
Distilled water

Dinner

45 g meat (beef topside lean only) roast
75 g peas (raw weight) (frozen or fresh)
100 g potato (raw weight)
100 g banana (flesh only)

Tea

Tea made with distilled water
5 g sugar
30 g Ryvita
15 g butter
15 g honey

Supper

40 g chicken
15 g lettuce
50 g tomato
100 g desert apple (flesh only)
30 g Ryvita
15 g butter

Bedtime

20 mls lemon juice
15 g sugar
Distilled water

36 g of Energen rolls can be used instead of 90 g Ryvita Distilled water for tea must be boiled in a special kettle or pan Old kettles contain fur

RESPONSIVITY TO PARATHORMONE (Ellsworth-Howard Test)

Parathyroid hormone increases urinary phosphate excretion if the patient is suffering from hypoparathyroidism It is difficult to demonstrate this effect in the normal subject

derive body area from height and weight are unsatisfactory in patients who are oedematous or of unusual shape

The apparatus must never be used on a tuberculous patient with acid-fast bacilli in the sputum as the machine cannot be thoroughly sterilized

INTERPRETATION

A range of -10 per cent to $+20$ per cent must be accepted as normal Some undoubted cases of myxoedema and thyrotoxicosis fall within this range One estimate of basal metabolic rate is unreliable the mean of three separate tests is more acceptable

The basal metabolic rate is raised in

- Anxiety states
- Thyrotoxicosis
- Fever
- Heart failure
- Anaemia and leukaemia
- Acromegaly
- Phaeochromocytoma

It is lowered in

- Endogenous depression
- Myxoedema
- Malnutrition
- Addison s disease

Calcium Metabolism

WARD TEST FOR URINARY CALCIUM

Sulkowitch solution is used made up as follows

- Oxalic acid 2 5 g
- Ammonium oxalate 2 5 g
- Glacial acetic acid 5 0 cc
- Distilled water to 150 cc.

5 cc of urine are placed in a test tube to which 2 cc of the solution are added The speed of appearance and the density of the resultant white dispersed precipitate are noted The results are recorded from zero to 4 plus A zero test suggests a serum calcium below 7 5 mg per cent. A 4 plus (heavy precipitate in under 20 seconds) suggests hypercalcaemia The test is only a rough approximation but useful for patients on calciferol therapy a 4 plus result indicates overdosage and requires immediate cessation of therapy until the serum calcium has been measured

drink of glucose The end of a successful test should always be marked by a big meal for the patient

INTERPRETATION

The normal subject (using 0 1 unit insulin/kg) exhibits a sharp fall in blood sugar maximal at 20 mins followed by a gradual rise until the level at 120 mins is within 5 per cent of the fasting value In hypopituitarism or primary adrenocortical failure hypoglycaemia is rapidly produced by *0 033 units insulin/kg and it persists so that at 120 minutes after injection* the blood-sugar is still below 80 per cent of the fasting value. This indicates hypoglycaemic unresponsiveness

There is seldom need to employ the test in cases of Addison s disease It has an important role in the diagnosis of panhypopituitarism Primary myxoedema does not produce the same pattern but is associated with a very slow fall in blood-sugar which will rise spontaneously As the test measures response to hypoglycaemia rather than sensitivity to insulin, a significant degree of hypoglycaemia must be induced before the test becomes valid

The Kepler Test

(of Robinson Power and Kepler)

This is based on the fact that in adrenocortical failure the body loses sodium chloride in the urine retains urea and is unable to respond to a water load by diuresis

PROCEDURE

On the day prior to the test no salt is added to the patient s diet From 6 0 p m onwards all food water and tobacco are withheld At 10 30 p m the bladder is emptied and the urine discarded All urine passed from then on up to and including emptying of the bladder at 7 30 a m is saved Omitting breakfast and following a further emptying of the bladder at 8 30 a m. the patient is given a draught of water to be drunk as quickly as possible The amount given is 9 cc per lb body weight (25 cc per kilo) The bladder is emptied at 9 30 a m 10 30 a m 11 30 a m and 12 30 p m the patient resting in bed meanwhile The volumes of all urine specimens are recorded The night sample is kept for analysis and a sample of blood is taken prior to the drinking of water

If the volume of the largest of the hourly day specimens exceeds that of the night urine volume then adrenocortical failure is not present

PROCEDURE

The patient fasts overnight and empties the bladder in the early morning (urine discarded) He then empties his bladder every hour for three hours The three specimens are saved for determination of phosphate concentration After the third sample has been passed 200 units of parathormone are injected intramuscularly (some prefer an intravenous injection) Hourly specimens of urine are passed over the succeeding five hours Water should be drunk during the test to keep up the flow of urine but no food should be eaten The phosphate concentration of all specimens is determined A rising phosphate concentration after the injection of parathyroid hormone indicates a normal response Unfortunately different preparations of parathormone vary in their capacity to promote phosphate diuresis A control test on a patient with known hypoparathyroidism is advisable for each batch of hormone

Insulin Tolerance Test

(Responsiveness to hypoglycaemia)

The return of the blood-sugar to normal levels from hypoglycaemia depends on the integrity of the anterior pituitary and the adrenal cortex The absence of such a response (i e continued hypoglycaemia) indicates adrenocortical or pituitary insufficiency

PROCEDURE

For at least four days prior to the test the diet must contain at least 250 g carbohydrate The fasting blood-sugar is determined and if it is normal the test can be carried out next day

The patient is fasted for twelve hours overnight blood is taken for a fasting blood-sugar determination Soluble insulin diluted with an adequate volume of normal saline is then injected intravenously The dose is 0 015 units per lb body weight (0 033 units per kilo) The blood-sugar is determined at 20 30 45 60 90 and 120 minutes after the injection If there is no fall in blood sugar with this dose of insulin the test is invalid and should be repeated at a later date using 0 45 units of insulin per lb body weight (0 1 units per kilo)

Difficulties The patient must be watched throughout the test for clinical evidence of hypoglycaemia Irrational or slurred speech and sweating are important signs The blood pressure should also be recorded at intervals If there is any clouding of consciousness or a fall of blood pressure below 80 mm Hg systolic the test is abandoned immediately by giving a large

is not followed by hormone release so that water diuresis continues unchecked

PROCEDURE

After a four hour deprivation of water food and tobacco the bladder is emptied and one litre of water is drunk as fast as possible Urine specimens are collected every ten minutes Complete emptying of the bladder requires a catheter (which is left in situ throughout the test) and supra pubic pressure When diuresis is established the urine flow exceeding 5 cc /minute nicotine is given Urine is collected as before and the effect on diuresis noted by recording the urine volumes throughout

For non smokers 1 mg of pure nicotine is injected intravenously in a normal saline solution On a subsequent test this can be increased to [illegible] mg if there is no response to the first dose For smokers 3 to 6 mg of nicotine are required An alternative to injection is the rapid smoking with deep inhalation of cigarettes until the patient feels sick and dizzy

Difficulties An overdose of nicotine causes fainting which is not only unpleasant for the patient but invalidates the test because of altered renal blood flow Therefore the initial dose should be low despite the difficulty of determining whether a lack of response is due to an insufficient dose or a damaged neurohypophysis

INTERPRETATION

Clear evidence of inhibition of the diuresis indicates an intact hypothalamus Continued diuresis with an adequate dose of nicotine indicates diabetes insipidus Unfortunately the distinction is not always clear cut as partial as well as complete lesions of the neurohypophysis can be found

Radio-Active Iodine in Diagnosis

PRINCIPLE

As the body does not distinguish between natural iodine and its radioactive isotopes tracing the fate of administered radio-iodine gives a clear picture of the physiological state of the thyroid s iodine cycle Alteration of thyroid function is mirrored by alterations in the iodine cycle thyrotoxicosis is associated with a rapid accumulation of a large proportion of available iodine with a consequent diminution in urinary excretion while in myxoedema thyroidal concentration of iodine is low and achieved slowly so that a large proportion of the element is slowly eliminated in the urine

If the volume of night urine exceeds that of any day specimen then urea and chloride in the plasma together with urea and chloride concentrations in the night urine are determined The following calculation is employed

$$\frac{\text{Urine Urea (mg per cent)}}{\text{Plasma urea (mg per cent)}} \times \frac{\text{Plasma Cl (mg per cent)}}{\text{Urine Cl (mg per cent)}} \times \frac{\text{Volume largest day urine (cc)}}{\text{Volume night urine (cc)}} = \text{Index}$$

As this mathematical device accentuates such disturbed function by multiplication it is apparent from the physiological principles involved that a low index number is found in adrenocortical failure If the index is less than 20 the diagnosis of adrenocortical insufficiency is likely

Difficulties The overnight fast may result in hypoglycaemia if the adrenal cortex is not functioning Furthermore the water load itself can cause headaches and even coma in Addison s disease or panhypopituitarism particularly if the serum chloride concentration is low

The presence of primary renal impairment invalidates the test Diabetes insipidus makes it virtually impossible to carry out the procedure Impaired water absorption in steatorrhoea or other small bowel disturbance and abnormal body water distribution as in oedematous states make interpretation very difficult

WATER LOADING TEST

A simplified procedure based on the principle of the Kepler test and subject to the same errors is the administration of one litre of water to the fasting subject and a record of the volume of urine passed in the succeeding four hours The normal subject will excrete about 70 per cent of the water load during this time Excretion of less than 50 per cent of the water is strongly suggestive of adrenocortical failure The test should be repeated after the administration of cortisone (100 mg injected I M on the night prior to the test) a marked increase in water diuresis from a previously inadequate level strengthens the original diagnosis of adrenocortical failure

Nicotine Stimulation of Neurohypophysis

PRINCIPLE

Nicotine causes the intact neurohypophysis to secrete vasopressin the effect of which is measured by its inhibition of water diuresis In lesions of the neurohypophysis leading to diabetes insipidus the giving of nicotine

The administration of any anti thyroid agent will invalidate the diagnostic use of radio-iodine nor should the patient be subjected to radiation unless a valid result can be expected. Iodides thyroid extract or the thiouracil group of drugs must have been stopped at least one month prior to the giving of radio-iodine More subtle sources of error arise from iodized cough lozenges or mixtures iodized ointments and the free use of iodine for skin sterilization. Very long lasting effects on the thyroid iodine cycle are caused by the iodized compounds used in the radiography of the renal and biliary tracts and arteriography A search for these sources of iodine must precede the request for a tracer dose of radio-iodine

The techniques outlined cannot give a direct answer to the clinical question of diagnosis They give an accurate answer to the question does this thyroid behave normally in terms of its iodine cycle The information given is related solely to function and not to underlying pathology Used properly radio-iodine is an important diagnostic aid whenever the clinical state suggests hyper- or hypothyroidism

The radiation danger to the patient is minimal but radio-iodine should only be given when the information required is of vital importance Repeated tests rapidly increase the risks Finally it is inadvisable to give the isotope to any pregnant woman, as the foetal thyroid concentrates iodine from the maternal blood stream

Urinary Steroid Estimations

17 ketosteroids are metabolites of adrenocortical and testicular C19 steroids whose physiological action is androgenic Small amounts of 17 ketosteroids are derived from C21 adrenal steroids with glucocorticoid properties The technique of measurement is reliable and reasonably free from difficulties An accurate 24-hour sample of urine is required The necessity for acid preservatives depends on the method the sample should be collected in bottles provided specially by the laboratory

The range of normal daily excretion is 10-20 mg for men, 6-18 mg for women Children of both sexes prior to puberty excrete insignificant amounts (1 mg or less) A marked decrease in excretion is typical of panhypopituitarism in both sexes and primary adrenal failure in women Liver disease malnutrition, chronic illness and hypothyroidism are all diseases which lower the excretion of 17 ketosteroids A marked increase is found in adrenal virilism but not in Cushing's syndrome The diagnostic use of the estimation is really restricted to panhypopituitarism

PROCEDURE

The radio-active isotope (administered free of natural iodine I^{127}) in common use is I^{131} with a half-life of 8 days For very short term studies I^{132} is of use with its half-life of 2 4 hours The radiation from these isotopes is measured by Geiger-Muller tubes or scintillation counters operated with electronic recording devices Unfortunately the great variety of apparatus used in numerous ways prevents any standardization of technique in consequence each laboratory has to define its own limits of normality and the significance of abnormal recordings

The dose of I^{131} for diagnostic studies is in the range of 10-50 micro-curies the radiation from this will not alter thyroid function or harm the patient Thyroidal accumulation of iodine can be measured by determining the amount of radiation in the neck at varying times after the do e It is preferable to have sufficient records to allow a calculation of the rate of accumulation as well as the amount of the dose retained By comparing the ratio of neck radiation to that of thigh or calf it is possible to guage the speed of iodine disappearance from the blood stream in relation to thyroid uptake Measurement of urinary excretion can be made on serial specimens of urine so that the rate of excretion as well as the amount of iodine excreted can be determined Small amounts of iodine excreted within the first few hours after administration are typical of thyrotoxicosis compared to the slow continued excretion of large amounts in myxoedema

Interpretation of these tests rests on the assumption that the activity of the thyroid iodine-trapping mechanism reflects the whole of thyroid function In every day clinical practice this assumption is correct but it does not hold good in cases of goitrous cretinism or with thyroids extremely deficient in iodine A more direct measure of hormone formation is the measurement of the I^{131} bound to protein in the blood 48 hours after the administration of a tracer dose The method has its share of technical difficulties but a high level indicates thyrotoxicosis no clear distinction can be made between normality and myxoedema

Difficulties Errors arise from problems of instrumentation and from the administration of anti thyroid agents prior to the test The clinician must state clearly whether the procedure is required to differentiate hypothyroidism from normality or to detect thyrotoxicosis This enables the laboratory to employ a technique relevant to the appropriate condition, because the difference in time relationships between the iodine cycle of hypothyroidism and thyrotoxicosis are such that the timing of measurements must be suited to the condition wh ch is being investigated

SUGGESTIONS FOR FURTHER READING

THERE are a great number of books published in various countries which deal with endocrinology in general and with special aspects of the subject. If the choice is limited to general textbooks of clinical endocrinology published in England the following books are recommended

The Practice of Endocrinology R Greene 2nd Edition 1951 (Eyre & Spottiswoode)

Major Endocrine Disorders S L Simpson 2nd Edition 1948 (Oxford University Press)

Clinical Endocrinology A W Spence 1st Edition 1953 (Cassell & Co)

The background of chemistry and physiology which is necessary for a full understanding of clinical endocrinology is covered fully in two volumes entitled

The Hormones G Pincus and K V Thimann 1st Edition 1948 (Academic Press)

For those who wish to refer to a compilation of original articles there is a massive survey of the literature in

Clinical Endocrinology L M Hurxthal and N Musulin 1st Edition 1953 (J B Lippincott)

The pharmacology and therapeutics of endocrine disorders is detailed with great lucidity in the appropriate sections of

The Pharmacological Basis of Therapeutics L S Goodman and A Gilman 2nd Edition 1955 (Macmillan)

Even the briefest account of the literature would be inadequate without some guide to the publications which will carry the results of future research The periodic publication of *Recent Advances in Endocrinology* (current edition (the 7th) edited by P M F Bishop 1954 Churchill) covers this field Excellent annual reviews of various endocrine subjects will be found in *Vitamins and Hormones* (first published 1943 Academic Press) and *Recent Progress in Hormone Research* (first published 1947 Academic Press) The available volumes of these publications contain a mine of information. In addition to these the *Colloquia on Endocrinology* (Ciba Foundation) the eighth volume being published in 1955 provide discussions of a high academic level.

adrenal virilism and Addison's disease in women An increase in 17 ketosteroid output following 4-5 days of A C T H administration is a useful guide to the integrity of the adrenal cortex

Methods for measuring the metabolites of hydrocortisone are subject to considerable technical difficulties and are both unreliable and non-specific However, high values support a diagnosis of Cushing's syndrome whether the method measures 17 ketogenic steroids (by sodium bismuthate treatment) or formaldehydogenic steroids (periodic acid liberates formaldehyde) or neutral lipid soluble reducing steroids All results must be interpreted with caution None of these methods should be attempted by a laboratory which cannot afford the skill and time required for accurate standardization of the technique

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Many medical journals contain original work in the field of endocrinology *The Journal of Clinical Endocrinology and Metabolism* (published monthly in U S A) is devoted to articles of clinical importance However the *Lancet* and the *British Medical Journal* report all important advances in the subject either in original articles or in their excellent annotations

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